

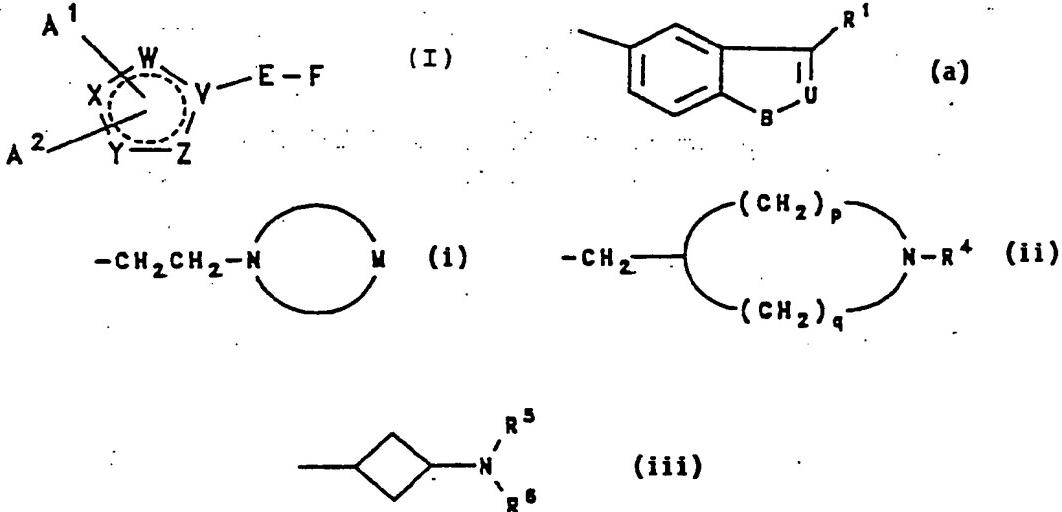
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(54) Title: IMIDAZOLE, TRIAZOLE AND TETRAZOLE DERIVATIVES



(57) Abstract

Imidazole, triazole and tetrazole derivatives of formula (I) are selective agonists of 5-HT₁-like receptors and are therefore useful in the treatment of clinical conditions, in particular migraine and associated disorders, for which a selective agonist of these receptors is indicated, wherein the broken circle represents two non-adjacent double bonds in any position in the five-membered ring; two, three or four of V, W, X, Y and Z represent nitrogen and the remainder represent carbon provided that, when two of V, W, X, Y and Z represent nitrogen and the remainder represent carbon, then the said nitrogen atoms are in non-adjacent positions within the five-membered ring; E represents a bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms; F represents a group of formula (a); U represents nitrogen or C-R²; B represents oxygen, sulphur or N-R³; R¹ represents a group of formula (i), (ii) or (iii).

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IMIDAZOLE, TRIAZOLE AND TETRAZOLE DERIVATIVES

5 The present invention relates to a class of substituted imidazole, triazole and tetrazole derivatives which act on 5-hydroxytryptamine (5-HT) receptors, being selective agonists of so-called "5-HT₁-like" receptors. They are therefore useful in the treatment of clinical conditions for which a selective agonist of these receptors is indicated.

10 5-HT₁-like receptor agonists which exhibit selective vasoconstrictor activity have recently been described as being of use in the treatment of migraine (see, for example, A. Doenicke *et al.*, *The Lancet*, 1988, Vol. 1, 1309-11). The compounds of the present

15 invention, being selective 5-HT₁-like receptor agonists, are accordingly of particular use in the treatment of migraine and associated conditions, e.g. cluster headache, chronic paroxysmal hemicrania, headache associated with vascular disorders, tension headache and paediatric migraine.

20 EP-A-0313397 and WO-A-91/18897 describe separate classes of tryptamine derivatives substituted by various five-membered heteroaliphatic rings, which are stated to be specific to a particular type of "5-HT₁-like" receptor and thus to be effective therapeutic agents for the treatment of clinical conditions, particularly migraine, requiring this activity. However, neither EP-A-0313397 nor WO-A-91/18897 discloses or suggests the imidazole, triazole and tetrazole derivatives provided by the present invention.

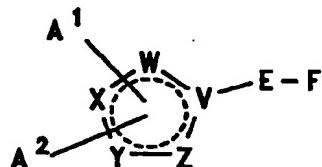
25 EP-A-0497512, published on 5th August 1992, describes a class of substituted imidazole, triazole and tetrazole derivatives which are stated to be selective agonists of 5-HT₁-like receptors and hence to be of

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particular use in the treatment of migraine and associated conditions.

The present invention provides a compound of formula I, or a salt or prodrug thereof:

5



(1)

wherein the broken circle represents two non-adjacent double bonds in any position in the five-membered ring;

15 two, three or four of V, W, X, Y and Z represent nitrogen and the remainder represent carbon provided that, when two of V, W, X, Y and Z represent nitrogen and the remainder represent carbon, then the said nitrogen atoms are in non-adjacent positions within
20 the five-membered ring;

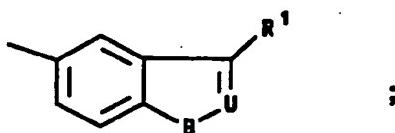
A¹ represents hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, -OR^X, -SR^X, -NR^XRY, -NR^XCORY, -NR^XCO₂RY, -NR^XSO₂RY, or -NR^ZCTNR^XRY;

25 A² represents a non-bonded electron pair when four of V, W, X, Y and Z represent nitrogen and the other represents carbon; or, when two or three of V, W, X, Y and Z represent nitrogen and the remainder represent carbon, A² represents hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, -OR^X, -SR^X, -NR^XRY, -NR^XCORY, -NR^XCO₂RY, -NR^XSO₂RY, or -NR^ZCTNR^XRY;

E represents a bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;

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F represents a group of formula

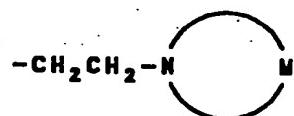


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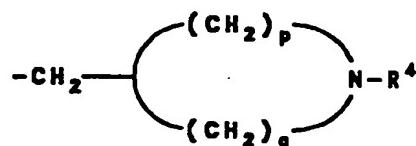
U represents nitrogen or C-R²;

B represents oxygen, sulphur or N-R³;

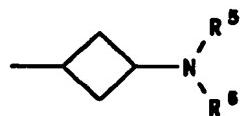
R¹ represents a group of formula (i), (ii) or
(iii):



(i)



(ii)



(iii)

30

in which

M represents the residue of an azetidine,
pyrrolidine or piperidine ring;

p is zero or 1 and q is an integer from 1 to 4,
provided that the sum of p+q is 2, 3 or 4;

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R², R³, R⁴, R⁵ and R⁶ independently represent hydrogen or C₁₋₆ alkyl;

5 R^X and R^Y independently represent hydrogen, hydrocarbon or a heterocyclic group, or R^X and R^Y together represent a C₂₋₆ alkylene group;

R^Z represents hydrogen, hydrocarbon or a heterocyclic group;

T represents oxygen, sulphur or a group of formula =N.G; and

10 G represents hydrocarbon, a heterocyclic group or an electron-withdrawing group.

The present invention also provides compounds of formula I above wherein R¹ represents a group of formula (i) or (ii), and the remaining substituents are 15 as defined above.

For use in medicine, the salts of the compounds of formula I will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the 20 invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, sulphuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. 25 Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g.

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calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The term "hydrocarbon" as used herein includes straight-chained, branched and cyclic groups containing up to 18 carbon atoms, suitably up to 15 carbon atoms, and conveniently up to 12 carbon atoms. Suitable hydrocarbon groups include C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl and aryl(C₁₋₆)alkyl.

The expression "a heterocyclic group" as used herein includes cyclic groups containing up to 18 carbon atoms and at least one heteroatom preferably selected from oxygen, nitrogen and sulphur. The heterocyclic group suitably contains up to 15 carbon atoms and conveniently up to 12 carbon atoms, and is preferably linked through carbon. Examples of suitable heterocyclic groups include C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, heteroaryl and heteroaryl(C₁₋₆)alkyl groups.

Suitable alkyl groups include straight-chained and branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl and butyl groups. Particular alkyl groups are methyl, ethyl and t-butyl.

Suitable alkenyl groups include straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl and allyl groups.

Suitable alkynyl groups include straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

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Suitable cycloalkyl groups include groups containing from 3 to 7 carbon atoms. Particular cycloalkyl groups are cyclopropyl and cyclohexyl.

A particular aryl group is phenyl.

5 Particular aryl(C₁₋₆)alkyl groups include benzyl, phenethyl and phenylpropyl.

Suitable heterocycloalkyl groups include azetidinyl, pyrrolidyl, piperidyl, piperazinyl and morpholinyl groups.

10 Suitable heteroaryl groups include pyridyl, quinolyl, isoquinolyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, furyl, benzofuryl, dibenzofuryl, thiienyl, benzthienyl, imidazolyl, oxadiazolyl and thiadiazolyl groups.

15 Particular heteroaryl(C₁₋₆)alkyl groups include pyridylmethyl and pyrazinylmethyl.

The hydrocarbon and heterocyclic groups may in turn be optionally substituted by one or more groups selected from C₁₋₆ alkyl, adamantyl, phenyl, halogen, 20 C₁₋₆ haloalkyl, C₁₋₆ aminoalkyl, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, aryloxy, keto, C₁₋₃ alkyleneoxy, nitro, cyano, carboxy, C₂₋₆ alkoxy carbonyl, C₂₋₆ alkoxy carbonyl(C₁₋₆)alkyl, C₂₋₆ alkylcarbonyloxy, arylcarbonyloxy, C₂₋₆ alkylcarbonyl, arylcarbonyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulphanyl, C₁₋₆ alkylsulphonyl, arylsulphonyl, NR^VR^W, -NR^VCOR^W, -NR^VCO₂R^W, -NR^VSO₂R^W, -CH₂NR^VSO₂R^W, -NHCONR^VR^W, -CONR^VR^W, -SO₂NR^VR^W and -CH₂SO₂NR^VR^W, in which R^V and R^W independently represent hydrogen, C₁₋₆ alkyl, aryl or aryl(C₁₋₆)alkyl, or R^V and R^W together represent a C₂₋₆ alkylene group.

When R^X and R^Y, or R^V and R^W, together represent a C₂₋₆ alkylene group, this group may be an ethylene, propylene, butylene, pentamethylene or

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hexamethylene group, preferably butylene or pentamethylene.

When the group G represents an electron-withdrawing group, this group is suitably cyano, nitro, 5 -COR^X, -CO₂R^X or -SO₂R^X, in which R^X is as defined above.

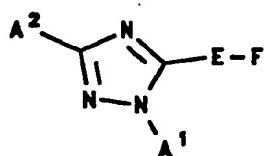
The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluorine.

10 The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible in vivo into the required compound of formula I. Conventional procedures for the selection and preparation 15 of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

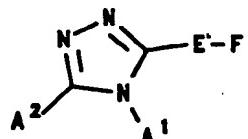
Where the compounds according to the invention have at least one asymmetric centre, they may accordingly 20 exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. In addition, the compounds of formula I above wherein R¹ represents a group of formula (iii) may exist as discrete 25 isomers in which the -NR⁵R⁶ group is either cis or trans to the other substituent on the cyclobutane ring. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

30 It will be appreciated that the imidazole, triazole and tetrazole rings of formula I can exist in a variety of isomeric forms having differing substitution patterns. These may suitably be represented by formulae IA to IT as follows:

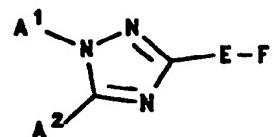
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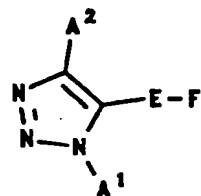
(IA)



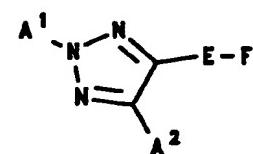
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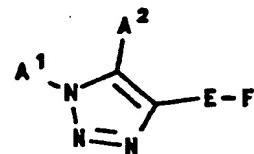
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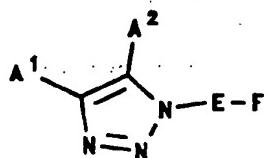
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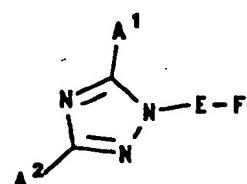
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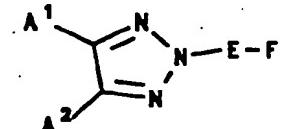
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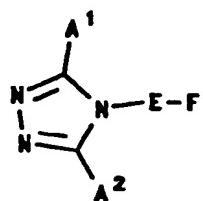


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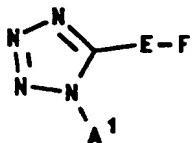


(IJ)

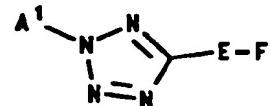
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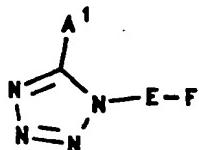
(I K)



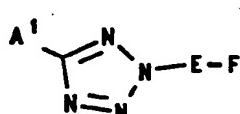
(I L)



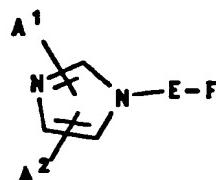
(I M)



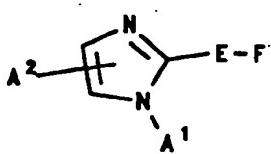
(I N)



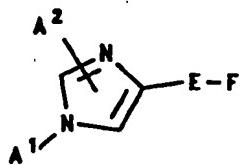
(I P)



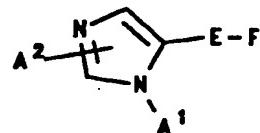
(I Q)



(I R)



(I S)



(I T)

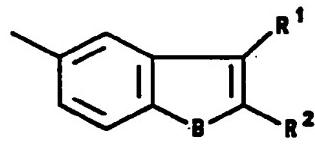
wherein A¹, A², E and F are as defined above. Preferred imidazole, triazole and tetrazole rings of formula I include the rings represented by formulae IA, IC, IG, IH, IK, IL, IM, IN, IP and IQ above, especially IH or IK.

The alkylene chain E may be, for example, methylene, ethylene, 1-methylethylene, propylene or

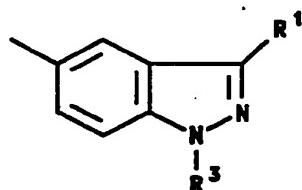
- 10 -

2-methylpropylene. Alternatively, the group E may represent a single bond such that the group F in formula I is attached directly to the five-membered heteroaromatic ring.

5 The group F is suitably an indole, benzofuran or benzothiophene moiety of formula FA, or an indazole moiety of formula FB:



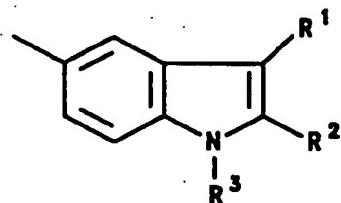
(FA)



(FB)

wherein B, R¹, R² and R³ are as defined above.

Preferably, the group F represents an indole moiety of structure FC:



(FC)

wherein R¹, R² and R³ are as defined above, in particular wherein R² and R³ are both hydrogen.

It will be appreciated that when four of V, W,
30 X, Y and Z represent nitrogen and the other represents carbon, i.e. when the ring of formula I is a tetrazole ring, then the group A² will be a non-bonded electron pair. Otherwise, A¹ and A² will independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen,

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cyano, trifluoromethyl, -OR^X, -SR^X, -NR^XRY, -NR^XCORY,
-NR^XCO₂RY, -NR^XSO₂RY, or -NR^ZCTNR^XRY.

Suitable values for the groups A¹ and/or A² include C₁-6 alkyl, C₃-7 cycloalkyl, aryl,
5 aryl(C₁-6)alkyl, C₃-7 heterocycloalkyl, heteroaryl,
heteroaryl(C₁-6)alkyl, C₁-6 alkoxy or C₁-6 alkylthio, any
of which groups may be optionally substituted; and
hydrogen, halogen, cyano, trifluoromethyl or -NR^XRY, in
which R^X and R^Y are as defined above. Examples of
10 optional substituents on the groups A¹ and/or A² suitably
include trifluoromethyl, C₁-6 alkoxy, C₂-6
aloxycarbonyl, C₂-6 alkylcarbonyl, C₁-6 alkylsulphonyl,
arylsulphonyl, amino, mono- or di(C₁-6)alkylamino, C₂-6
alkylcarbonylamino, arylcarbonylamino, C₂-6
15 alkoxycarbonylamino, C₁-6 alkylsulphonylamino, arylsulphonylamino, C₁-6
arylsulphonylamino, C₁-6 alkylsulphonylaminomethyl,
aminocarbonylamino, mono- or
di(C₁-6)alkylaminocarbonylamino, mono- or
diarylaminocarbonylamino, pyrrolidylcarbonylamino,
20 aminocarbonyl, mono- or di(C₁-6)alkylaminocarbonyl, C₁-6
alkylaminosulphonyl, aminosulphonylmethyl, and mono- or
di(C₁-6)alkylaminosulphonylmethyl.

Particular values of A¹ and/or A² include
hydrogen, methyl, methoxymethyl, aminomethyl,
25 dimethylaminomethyl, acetylaminomethyl,
benzoylaminomethyl, t-butoxycarbonylaminomethyl,
methylsulphonylaminomethyl, phenylsulphonylaminomethyl,
aminocarbonylmethyl, ethyl, aminoethyl, acetylaminoethyl,
benzoylamoethyl, methoxycarbonylamoethyl,
ethoxycarbonylamoethyl, t-butoxycarbonylamoethyl,
30 methylsulphonylamoethyl, aminocarbonylamoethyl,
methylaminocarbonylamoethyl, t-butylaminocarbonyl-
aminoethyl, phenylaminocarbonylamoethyl,
pyrrolidylcarbonylamoethyl, cyclopropyl, phenyl,

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methysulphonylaminophenyl, aminocarbonylphenyl,
methylaminocarbonylphenyl, methysulphonylaminomethyl-
phenyl, aminosulphonylmethylphenyl, methylaminosulphonyl-
methylphenyl, dimethylaminosulphonylmethylphenyl, benzyl,
5 trifluoromethylbenzyl, methoxybenzyl, acetylaminobenzyl,
methysulphonylaminobenzyl, aminocarbonylaminobenzyl,
aminocarbonylbenzyl, methylaminocarbonylbenzyl,
methysulphonylbenzyl, methylaminosulphonylbenzyl,
pyridylmethyl, methoxypyridylmethyl, amino, methylamino,
10 benzylamino, dimethylamino, t-butoxycarbonylamino-
ethylamino and methysulphonylaminooethylamino.

Preferred values of A¹ and/or A² include
hydrogen, methyl, ethyl and amino.

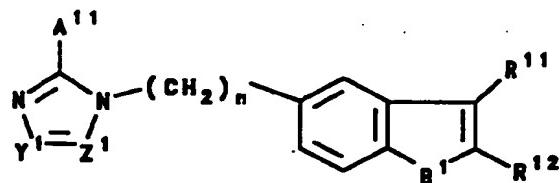
When R¹ represents a group of formula (ii), the
15 resulting group is an azetidin-2-ylmethyl, azetidin-3-
ylmethyl, pyrrolidin-2-ylmethyl, pyrrolidin-3-ylmethyl,
piperidin-2-ylmethyl or piperidin-3-ylmethyl group, in
particular an azetidin-3-ylmethyl or pyrrolidin-2-
ylmethyl group, substituted on the ring nitrogen atom by
20 the group R⁴.

In a particular embodiment, R¹ represents a
group of formula (i) in which M represents the residue of
an azetidine or pyrrolidine ring. Thus, R¹ suitably
represents the azetidin-1-ylethyl or pyrrolidin-1-ylethyl
moiety.
25

Preferred values for the groups R², R³, R⁴, R⁵
and R⁶ include hydrogen and methyl.

A particular sub-class of compounds according
to the invention is represented by the compounds of
30 formula II, and salts and prodrugs thereof:

- 13 -



(III)

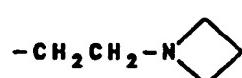
wherein

- 10 y^1 represents nitrogen or $A^{12}-C$;
- z^1 represents nitrogen or CH;
- n is zero, 1, 2 or 3;
- B^1 represents oxygen, sulphur or $N-R^{13}$;
- A^{11} and A^{12} independently represent C_{1-6} alkyl,
- 15 C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino or di(C_{1-6})alkylamino, any of which groups may be optionally substituted; or hydrogen, halogen, cyano,
- 20 trifluoromethyl or amino;
- R^{11} represents a group of formula (iv), (v), (vi), (vii) or (viii):

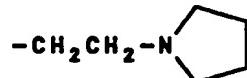
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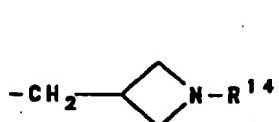
- 14 -



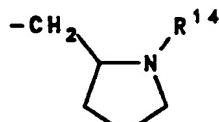
(iv)



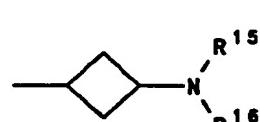
(v)



(vi)



(vii)



(viii)

15 and R^{12} , R^{13} , R^{14} , R^{15} and R^{16} independently represent hydrogen or C_{1-6} alkyl.

Examples of optional substituents on the groups A^{11} and A^{12} suitably include trifluoromethyl, C_{1-6} alkoxy, C_{2-6} alkoxy carbonyl, C_{2-6} alkyl carbonyl, C_{1-6} alkylsulphonyl, arylsulphonyl, amino, mono- or di(C_{1-6})alkylamino, C_{2-6} alkylcarbonylamino, arylcarbonylamino, C_{2-6} alkoxy carbonylamino, C_{1-6} alkylsulphonylamino, arylsulphonylamino, C_{1-6} alkylsulphonylaminomethyl, aminocarbonylamino, mono- or di(C_{1-6})alkylamino-carbonylamino, mono- or diarylaminocarbonylamino, pyrrolidyl carbonylamino, aminocarbonyl, mono- or di(C_{1-6})alkylaminocarbonyl, C_{1-6} alkylaminosulphonyl, aminosulphonylmethyl, and mono- or di(C_{1-6})alkyl-aminosulphonylmethyl.

30 Particular values of A^{11} and A^{12} with respect to formula II include hydrogen, methyl, ethyl and amino, especially hydrogen.

Preferably, R^{12} and R^{13} each represents hydrogen. Preferably, R^{14} is methyl.

- 15 -

Suitably, R¹⁵ and R¹⁶ are independently selected from hydrogen and methyl. Preferably, R¹⁵ and R¹⁶ are both methyl.

Specific compounds within the scope of the present invention include:

- 5 N-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethylazetidine;
 N-2-[5-(1,2,4-triazol-1-yl)-1H-indol-3-yl]ethylazetidine;
 N-methyl-3-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-
10 yl]ethylazetidine;
 N-methyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-
 yl]methylpyrrolidine;
 (2R)-N-methyl-2-[5-(1,2,4-triazol-4-yl)-1H-indol-3-
 yl]methylpyrrolidine;
15 3-[cis-1-(N,N-dimethylamino)cyclobutan-3-yl]-5-(1,2,4-
 triazol-1-ylmethyl)-1H-indole;
 3-[trans-1-(N,N-dimethylamino)cyclobutan-3-yl]-5-(1,2,4-
 triazol-1-ylmethyl)-1H-indole;
 N-2-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]ethylazetidine;
20 N-2-[5-(1,2,4-triazol-4-yl)-1H-indol-3-
 yl]ethylpyrrolidine;
 and salts and prodrugs thereof.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a

- 16 -

pharmaceutical carrier, e.g. conventional tabletting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous

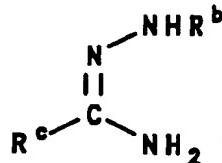
- 17 -

solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

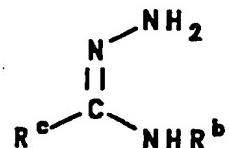
In the treatment of migraine, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

The 1,2,4-triazole compounds of this invention may be prepared by a process which comprises reacting a reactive derivative of a carboxylic acid of formula R^a-CO_2H with a compound either of formula III or of formula IV, or a salt thereof:

20



(III)



(IV)

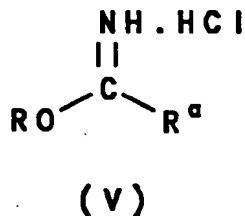
wherein one of R^a , R^b and R^c is a group of formula A^1 , another is a group of formula A^2 , and the third is a group of formula $-E-F$, as defined with reference to formula I above.

Suitable reactive derivatives of the acid R^a-CO_2H include esters, for example C₁₋₄ alkyl esters; thioesters, for example pyridylthioesters; acid

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anhydrides, for example $(R^a\text{-CO})_2\text{O}$; acid halides, for example acid chlorides; orthoesters; and primary, secondary and tertiary amides.

5 A preferred reactive derivative of the acid $R^a\text{-CO}_2\text{H}$ is the iminoether derivative of formula V:



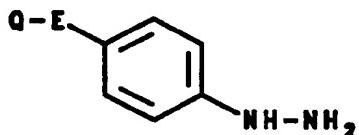
where R is C_{1-4} alkyl.

15 The reagent of formula III may be generated in situ in the reaction mixture. For example, the reaction may be effected by treating a compound of formula V above with an alkyl hydrazine, e.g. methyl hydrazine, followed by a suitable carboxylic acid such as formic acid.

20 The reaction is conveniently carried out by heating the reagents together, optionally in a solvent, for example tetrahydrofuran, dimethylformamide or a lower alkanol such as ethanol, propanol or isopropanol, at about 20°C to 100°C for about 1 to 6 hours.

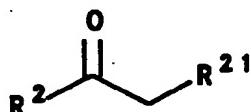
25 Where R^a is a group of formula -E-F and the group F is an indole moiety of structure FC as defined above, the reactive derivative of a carboxylic acid of formula $\text{HO}_2\text{C-E-F}$ may be prepared by reacting a compound of formula VI:

- 19 -



(VI)

wherein Q represents a reactive carboxylate moiety, and E is as defined above; with a compound of formula VII or a carbonyl-protected form thereof:



(VII)

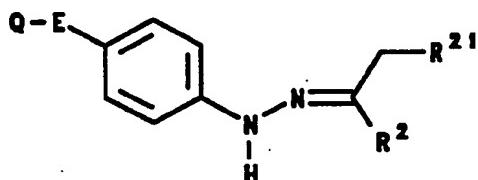
wherein R² is as defined above and R²¹ corresponds to the group R¹ as defined above or represents a protected derivative thereof; followed by removal of any protecting groups present; and subsequently, where required, N-alkylation by standard methods to introduce the moieties R³ and/or R⁴.

Suitable carbonyl-protected forms of the compounds of formula VII include the dimethyl acetal or ketal derivatives.

The reaction of compounds VI and VII may be carried out in a single step (Fischer indole synthesis) or by an initial non-cyclising step at a lower temperature to give a compound of formula VIII:

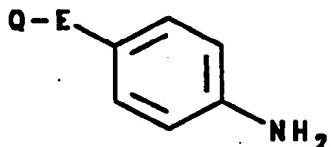
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- 20 -



wherein Q, E, R² and R²¹ are as defined above; followed
10 by cyclisation using a suitable reagent, such as a polyphosphate ester, to give a compound of formula Q-E-F.

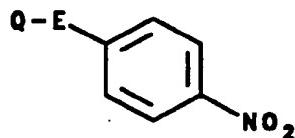
The hydrazines of formula VI may be prepared from the corresponding anilines of formula IX:



wherein Q and E are as defined above; by diazotisation followed by reduction. Diazotisation is typically carried out using sodium nitrite/conc. HCl and the resulting diazo product reduced *in situ* using, for
25 example, tin(II) chloride/conc. HCl, sodium sulphite/conc. HCl, or sodium sulphite/conc. H₂SO₄.

The anilines of formula IX may be prepared by reduction of the corresponding nitro compounds of formula X:

- 21 -

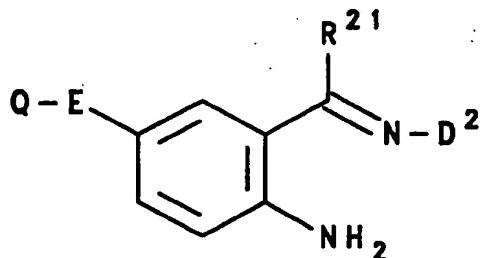


(X)

wherein Q and E are as defined above; typically by transfer hydrogenation using a hydrogenation catalyst such as palladium on charcoal in the presence of a hydrogen donor such as ammonium formate, or alternatively by conventional catalytic hydrogenation or using tin(II) chloride.

Where they are not commercially available, the nitro compounds of formula X may be synthesized by standard methods well known to those skilled in the art.

Where R^a is a group of formula -E-F and the group F is an indazole moiety of structure FB as defined above, the reactive derivative of a carboxylic acid of formula HO₂C-E-F may be prepared by the cyclisation of a compound of formula XI:



(XI)

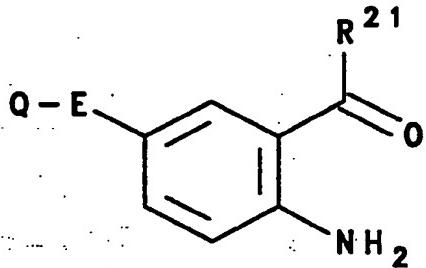
wherein Q, E and R²¹ are as defined above and D² represents a readily displaceable group; followed by

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removal of any protecting groups present; and subsequently, where required, N-alkylation by standard methods to introduce the moieties R³ and/or R⁴.

5 The cyclisation of compound XI is conveniently achieved in a suitable organic solvent at an elevated temperature, for example in a mixture of m-xylene and 2,6-lutidine at a temperature in the region of 140°C.

10 The readily displaceable group D² in the compounds of formula XI suitably represents a C₁₋₄ alkanoyloxy group, preferably acetoxy. Where D² in the desired compound of formula XI represents acetoxy, this compound may be conveniently prepared by treating a carbonyl compound of formula XII:

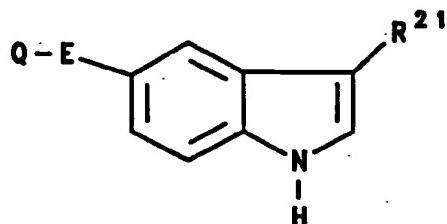


(XII)

25 wherein Q, E and R²¹ are as defined above; or a protected derivative thereof; with hydroxylamine hydrochloride, advantageously in pyridine at the reflux temperature of the solvent; followed by acetylation with acetic anhydride, advantageously in the presence of a catalytic quantity of 4-dimethylaminopyridine, in dichloromethane at room temperature.

30 The N-formyl protected derivative of the intermediate of formula XII may be conveniently prepared by ozonolysis of an indole derivative of formula XIII:

- 23 -



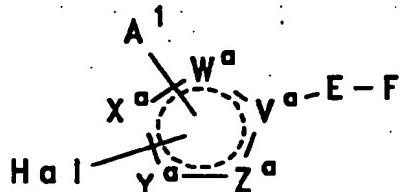
(XIII)

10 wherein Q, E and R²¹ are as defined above; followed by a reductive work-up, advantageously using dimethylsulphide.

The indole derivative of formula XIII may be prepared by methods analogous to those described in the accompanying Examples, or by procedures well known from 15 the art.

In an alternative process, the triazole compounds according to the invention may be prepared by a method which comprises reacting a compound of formula XIV:

20



(XIV)

wherein A¹, E and F are as defined above, Hal represents 30 halogen, and two of v^a, w^a, x^a, y^a and z^a, to one of which the group Hal is attached, represent carbon and the remainder represent nitrogen; with a reagent which provides an anion -A², where A² is as previously defined.

- 24 -

Reagents which may provide the anion ${}^{-}A^2$ include Grignard reagents A^2MgHal (where Hal = halogen); organocuprate reagents such as LiA^2_2Cu ; organolithium reagents A^2Li ; or compounds which stabilise the anion by means of an adjacent activating group such as an ester or enolisable ketone function. In this case, the adjacent ester or ketone function may be retained after the process is complete, or may be removed. For example, an ester moiety may be hydrolysed and decarboxylated.

The 1,2,3-triazole compounds according to the present invention may be prepared by a process which comprises the cycloaddition of an alkyne of formula $R^a-C\equiv C-R^b$ with an azide of formula R^c-N_3 , where R^a , R^b and R^c are as defined above.

The cycloaddition reaction may be conveniently effected in a suitable solvent such as tetrahydrofuran, ideally by heating in an autoclave for 8 hours.

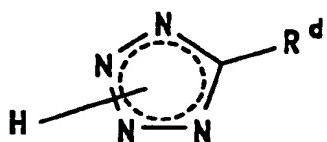
The tetrazole compounds in accordance with the invention may be prepared by a process which comprises the cycloaddition of a nitrile of formula $N=C-R^d$ with an azide of formula R^e-N_3 , where one of R^d and R^e represents a group of formula A^1 and the other is a group of formula $-E-F$, as defined previously.

The cycloaddition reaction is conveniently effected by heating the reactants together at an elevated temperature, e.g. a temperature in the region of $150^{\circ}C$, in a suitable solvent such as N-methylpyrrolid-2-one, advantageously in the presence of triethylamine hydrochloride. The product obtained from the cycloaddition reaction will generally be a mixture of isomers substituted by the A^1 group at positions 1 and 2 of the tetrazole ring, corresponding to structures IL and IM respectively as defined above. These isomers may

- 25 -

conveniently be separated using conventional techniques such as chromatography.

5 In an alternative process, the tetrazole compounds of the invention may be prepared by a method which comprises reacting a compound of formula R^e-L with a tetrazole derivative of formula XV:



(XV)

15 wherein one of R^d and R^e represents a group of formula A¹ and the other is a group of formula -E-F, as defined above, and L represents a suitable leaving group; in the presence of a base such as triethylamine.

20 The leaving group L suitably represents halogen, e.g. bromine or iodine, or a sulphonate derivative such as tosylate or mesylate.

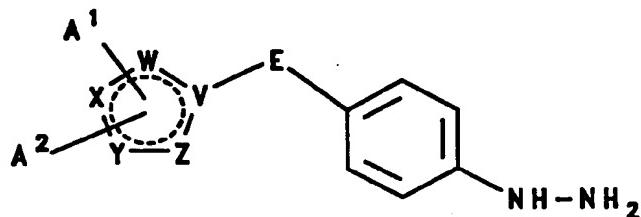
The reaction is conveniently carried out in a suitable organic solvent, e.g. acetonitrile, at room temperature.

25 The tetrazole derivatives of formula XV may be prepared by cycloaddition of a nitrile of formula N=C-R^d with sodium azide, advantageously under the conditions described above for the reaction between the nitrile N=C-R^d and the azide R^e-N₃; followed by acidification 30 with a mineral acid such as hydrochloric acid.

In a further process, the compounds according to the invention wherein the group F is an indole moiety of structure FC as defined above may be prepared by a

- 26 -

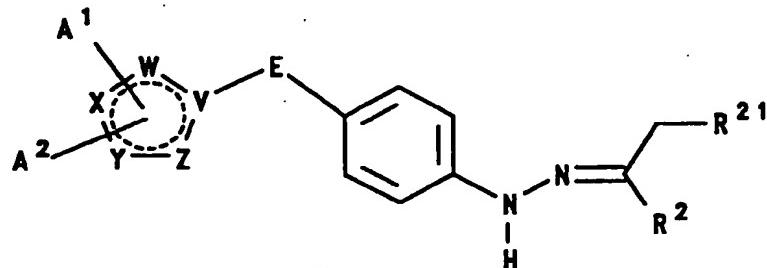
method which comprises reacting a compound of formula XVI:



(XVI)

wherein V, W, X, Y, Z, A¹, A² and E are as defined above; with a compound of formula VII as defined above, or a carbonyl-protected form thereof, e.g. the dimethyl acetal or ketal; followed by removal of any protecting groups present; and subsequently, where required, N-alkylation by standard methods to introduce the moieties R³ and/or R⁴.

As with that between compounds VI and VII, the reaction between compounds XVI and VII may be carried out in a single step (Fischer indole synthesis) or by an initial non-cyclising step at a lower temperature to give a compound of formula XVII:

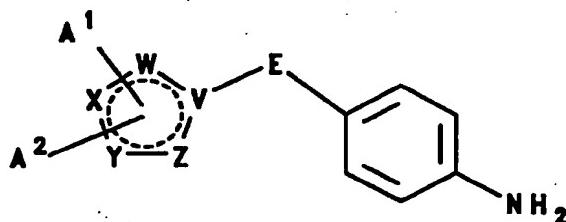


(XVII)

- 27 -

wherein V, W, X, Y, Z, A¹, A², E, R² and R²¹ are as defined above; followed by cyclisation using a suitable reagent, e.g. a polyphosphate ester.

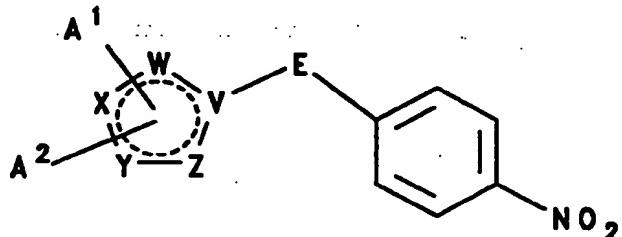
5 The hydrazines of formula XVI may be prepared from the corresponding anilines of formula XVIII:



(XVIII)

15 wherein V, W, X, Y, Z, A¹, A² and E are as defined above; by methods analogous to those described above with reference to the compounds of formula IX.

The anilines of formula XVIII may be prepared from the corresponding nitro compounds of formula XIX:



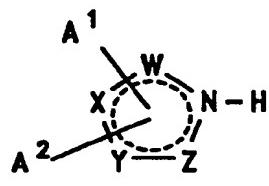
(XIX)

wherein V, W, X, Y, Z, A¹, A² and E are as defined above; by methods analogous to those described above with reference to the compounds of formula X.

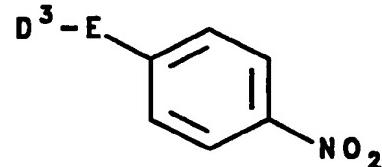
30 The nitro compounds of formula XIX may be prepared by a variety of methods which will be readily apparent to those skilled in the art. For example, where V represents a nitrogen atom, the relevant compounds of

- 28 -

formula XIX may be prepared by reacting the anion of a compound of formula XX with a compound of formula XXI:



(XX)



(XXI)

wherein W, X, Y, Z, A¹, A² and E are as defined above, and D³ represents a readily displaceable group.

- Where compound XX is a triazole or tetrazole derivative, the anion thereof may be generated by carrying out the reaction in a base such as triethylamine. Where compound XX is an imidazole derivative, the anion thereof may conveniently be generated if the reaction is carried out in the presence of sodium hydride using N,N-dimethylformamide as solvent.
- 15 Where salts of the compounds of formula XX are commercially available, e.g. the sodium salt of 1,2,4-triazole, these are advantageously utilised in N,N-dimethylformamide solution in place of the compounds of formula XX themselves, with no requirement in this instance for additional base to be present in the reaction mixture.
- 20 25

- The readily displaceable group D³ in the compounds of formula XXI is suitably a halogen atom, preferably bromine; except when the moiety D³ is attached directly to the aromatic ring, i.e. when E represents a bond, in which case D³ is preferably fluorine.

In an alternative approach, the compounds of formula XIX wherein the five-membered heteroaromatic ring is a 1,2,4-triazol-1-yl moiety and A¹ and A² are both

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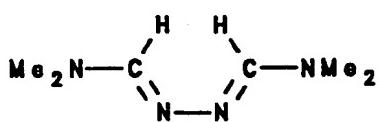
hydrogen may be prepared by reacting 4-amino-1,2,4-triazole with a compound of formula XXI as defined above, followed by deamination of the resulting 1-substituted 4-amino-4H-1,2,4-triazolium salt by treatment with nitrous acid and subsequent neutralisation. This transformation, which may be accomplished in two separate steps or advantageously as a "one-pot" procedure with both steps combined, is conveniently effected using reaction conditions analogous to those described in J. Org. Chem., 10 1989, 54, 731.

Where they are not commercially available, the nitro compounds of formula XXI above may be prepared by procedures analogous to those described in the accompanying Examples, or by methods well known from the art. 15

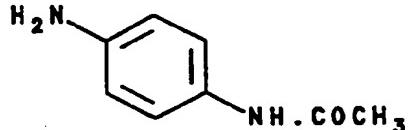
In an alternative approach to the 1,2,4-triazole derivatives, the nitro compounds of formula XIX may be prepared from those of formula X above by appropriate modification of the moiety Q using, for 20 example, methods analogous to those described above with reference to the compounds of formulae III and IV. Thus, for example, since Q in the compounds of formula X represents a reactive carboxylate moiety, the compounds of formula XIX may be prepared therefrom by reaction with a compound of formula $A^2-C(=NNHA^1)NH_2$ or $A^2-C(=NNH_2)NHA^1$. 25

Following a further representative pathway, the aniline derivatives of formula XVIII wherein the five-membered heteroaromatic ring is a 1,2,4-triazol-4-yl moiety, E is a bond and A^1 and A^2 are both hydrogen may 30 be prepared by reacting the hydrazine derivative of formula XXII with the acetanilide of formula XXIII:

- 30 -



(XXIII)



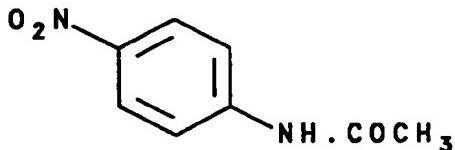
(XXIV)

followed by removal of the N-acetyl protecting group.

10 The reaction between compounds XXII and XXIII
is conveniently effected in refluxing toluene,
advantageously in the presence of a catalytic quantity of
p-toluenesulphonic acid. Subsequent removal of the N-
acetyl protecting group is typically effected in hot
15 aqueous 5N hydrochloric acid.

20 The hydrazine derivative of formula XXII can be
prepared from N,N'-diformylhydrazine by reaction with
thionyl chloride/N,N-dimethylformamide, as reported in J.
Chem. Soc. (C), 1967, 1664, and subsequent treatment with
sodium methoxide in methanol.

25 The acetanilide of formula XXIV may be
prepared by reduction of the corresponding nitro compound
of formula XXIV:



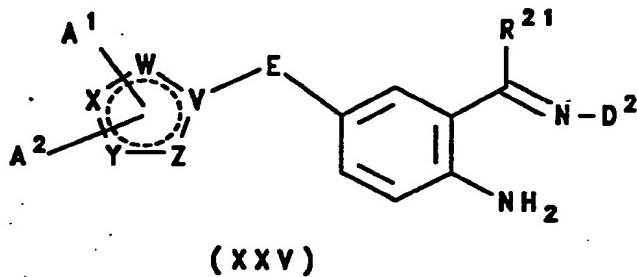
(XXV)

typically by transfer hydrogenation using a hydrogenation catalyst in the presence of a hydrogen donor such as ammonium formate, or alternatively by conventional catalytic hydrogenation or using tin(II) chloride.

- 31 -

The nitro compound of formula XXIV is commercially available from the Aldrich Chemical Company Ltd., Gillingham, United Kingdom.

5 In a still further process, the compounds according to the invention wherein the group F is an indazole moiety of structure FB as defined above may be prepared by a method which comprises cyclising a compound of formula XXV:

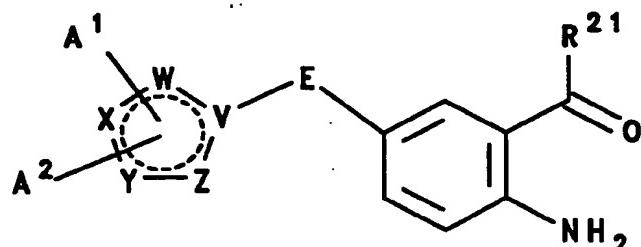


20 wherein V, W, X, Y, Z, A¹, A², E, R²¹ and D² are as defined above; followed by removal of any protecting groups present; and subsequently, where required, N-alkylation by standard methods to introduce the moieties R³ and/or R⁴.

25 As with the cyclisation of compound XI, that of compound XXV is conveniently achieved in a suitable organic solvent at an elevated temperature, for example in a mixture of m-xylene and 2,6-lutidine at a temperature in the region of 140°C.

30 The compounds of formula XXV may, for example, be prepared from the corresponding compound of formula XXVI:

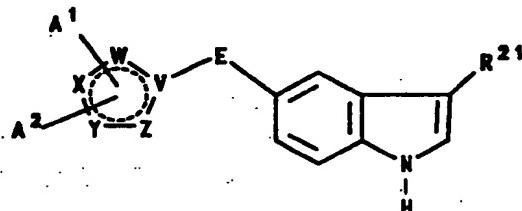
- 32 -



(XXVI)

wherein V, W, X, Y, Z, A¹, A², E and R²¹ are as defined above; or a protected derivative thereof; which in turn may be prepared from the corresponding compound of formula XXVII:

15



(XXVII)

wherein V, W, X, Y, Z, A¹, A², E and R²¹ are as defined above; using methods analogous to those described above with reference to the compounds of formulae XII and XIII. Thus, for example, since Q in the compounds of formula XIII represents a reactive carboxylate moiety, the 1,2,4-triazole derivatives of formula XXVII may be prepared therefrom by reaction with a compound of formula A²-C(=NNH^A¹)NH₂ or A²-C(=NNH₂)NHA¹.

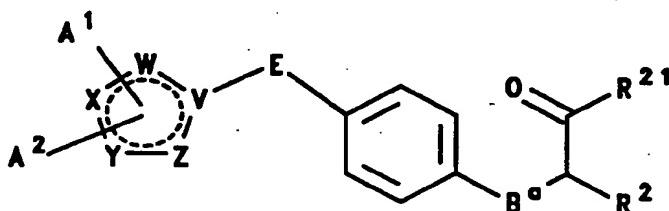
25

In a yet further process, the compounds according to the invention wherein the group F is a benzofuran or benzthiophene moiety may be prepared by a

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method which comprises cyclising a compound of formula XXVIII:

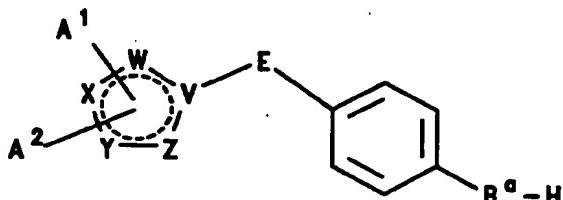


(XXVIII)

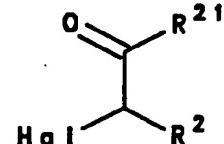
wherein V, W, X, Y, Z, A¹, A², E, R² and R²¹ are as defined above, and B^a represents oxygen or sulphur; followed by removal of any protecting groups present; and subsequently, where required, N-alkylation by standard methods to introduce the moiety R⁴.

The cyclisation is conveniently effected by using polyphosphoric acid or a polyphosphate ester, advantageously at an elevated temperature.

The compounds of formula XXVIII may be prepared by reacting a compound of formula XXIX with a compound of formula XXX:



(XXIX)



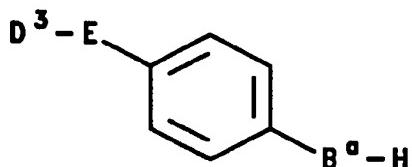
(XXX)

wherein V, W, X, Y, Z, A¹, A², E, B^a, R² and R²¹ are as defined above, and Hal represents halogen.

The reaction is conveniently effected in the presence of a base such as sodium hydroxide.

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5 The hydroxy and mercapto derivatives of formula XXIX may be prepared by a variety of methods which will be readily apparent to those skilled in the art. In one such method, the anion of a compound of formula XX as defined above is reacted with a compound of formula XXXI:



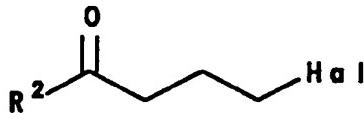
(XXXI)

15 wherein D³, E and B^a are as defined above; to afford an intermediate of formula XXIX wherein V is nitrogen.

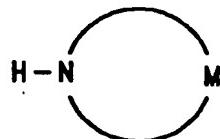
The compounds of formula XXX and XXXI, where they are not commercially available, may be prepared by standard procedures well known in the art.

20 The intermediates of formula VII wherein R²¹ represents a group of formula (i) as defined above with reference to R¹, or the carbonyl-protected forms thereof, may conveniently be prepared by reacting a compound of formula XXXII, or a carbonyl-protected form thereof, with a compound of formula XXXIII:

25



(XXXII)



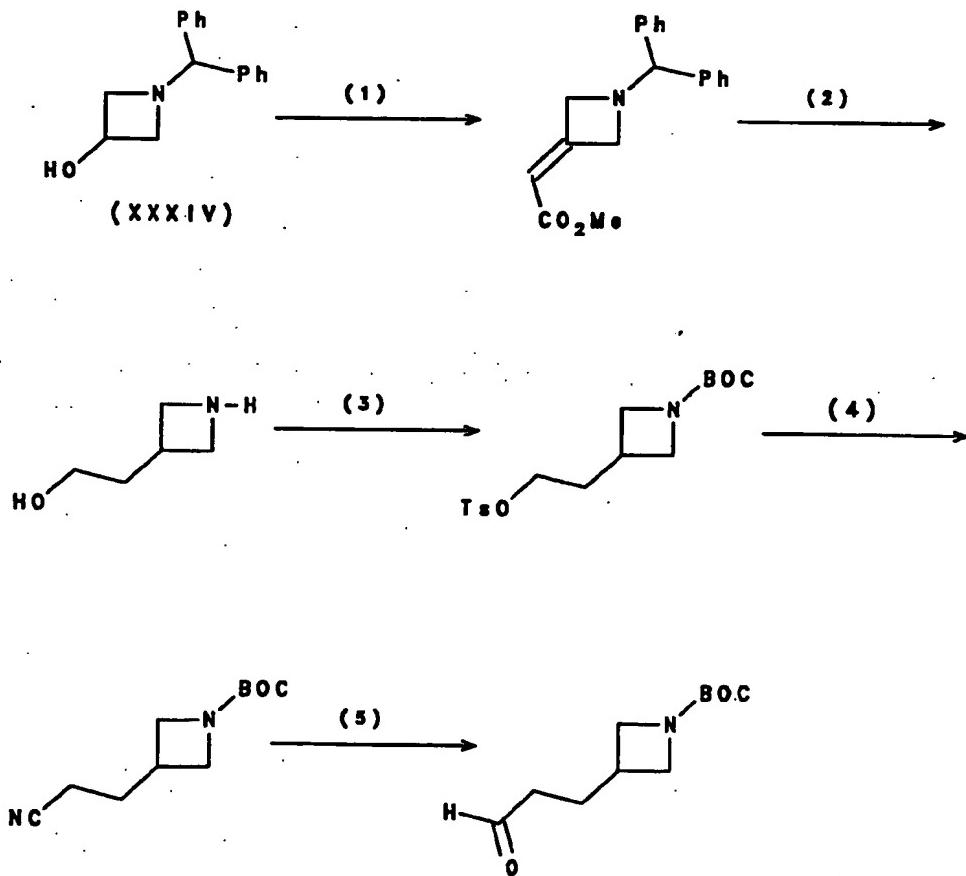
(XXXIII)

wherein R² and M are as defined above; and Hal represents halogen, especially chlorine. The reaction is suitably

- 35 -

carried out in the presence of a base such as potassium carbonate, typically in a solvent such as N,N-dimethylformamide.

5 The preparation of a typical intermediate of formula VII, wherein R²¹ represents an azetidin-3-ylmethyl moiety protected on the ring nitrogen atom by a t-butoxycarbonyl (BOC) group, is illustrated by the following reaction scheme:

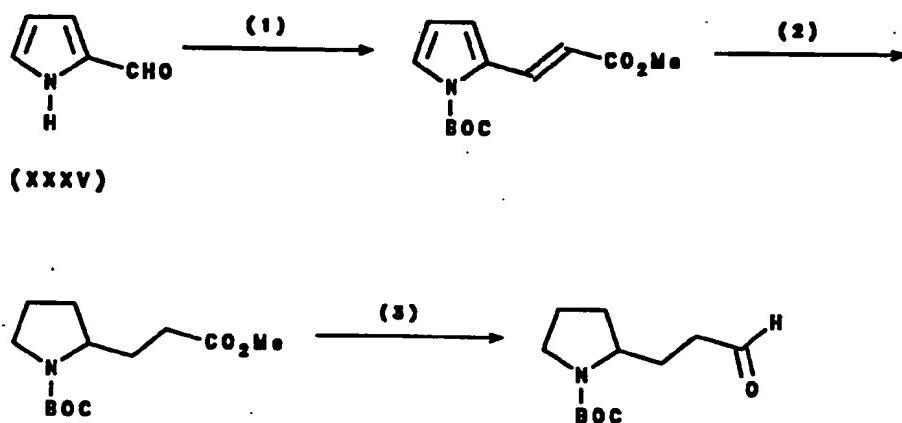


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The starting compound XXXIV is known from J. Chem. Soc., Chem Commun., 1968, 93. Step 1 of the reaction scheme comprises oxidation of the hydroxy group of compound XXXI to a carbonyl group using pyridine. SO_3 in dimethyl sulphoxide (DMSO) and triethylamine; followed by reaction of the resulting azetidinone derivative with the Horner-Emmons reagent $\text{MeO}_2\text{C}.\text{CH}_2.\text{PO}(\text{OEt})_2$ in the presence of sodium hydride, using tetrahydrofuran (THF) as the solvent. In Step 2, the double bond of the azetidine olefin ester is hydrogenated over palladium-charcoal in methanol; the methyl ester group is then reduced to hydroxymethyl by treatment with lithium aluminium hydride in THF; and the diphenylmethyl protecting group is in turn removed by treatment with palladium hydroxide on charcoal, with methanol serving as the solvent. Step 3 involves protection of the azetidine nitrogen as the N-t-butoxycarbonyl (N-BOC) carbamate derivative; followed by conversion of the primary hydroxy group to tosyloxy by reaction with p-toluenesulphonyl chloride (tosyl chloride, TsCl) in pyridine/dichloromethane. Displacement of the tosyloxy group by cyanide ion in Step 4 is followed in Step 5 by reduction of the resulting cyano compound to the corresponding aldehyde derivative using diisobutylaluminium hydride (DIBAL-H) in THF, with an ammonium chloride work-up.

The preparation of a further typical intermediate of formula VII, in which R^{21} represents a pyrrolidin-2-ylmethyl moiety protected on the ring nitrogen atom by a BOC group, is illustrated by the following reaction scheme:

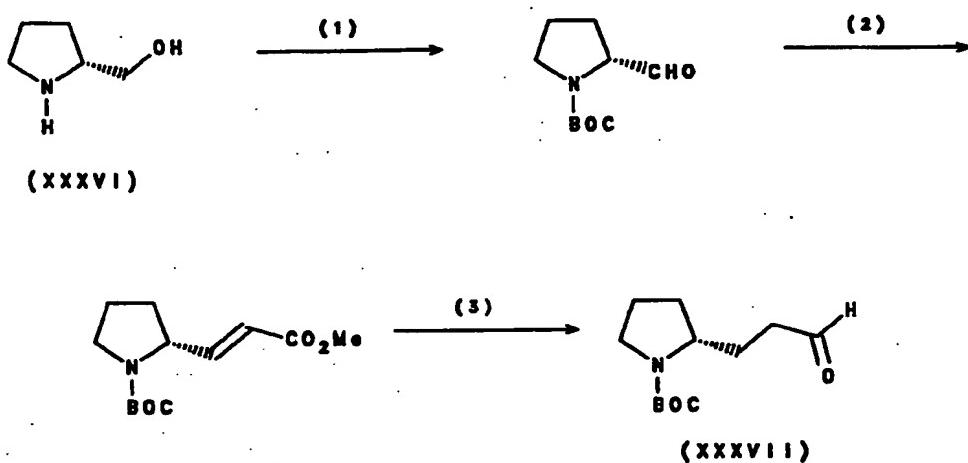
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The starting compound XXXV is commercially available from Aldrich Chemical Company Ltd., Gillingham, U.K. Step 1 of the reaction scheme involves protection of the pyrrole nitrogen as the N-t-butoxycarbonyl (N-BOC) carbamate derivative; followed by reaction of the formyl moiety in the 2-position with the Horner-Emmons reagent $\text{MeO}_2\text{C} \cdot \text{CH}_2 \cdot \text{PO}(\text{OEt})_2$ in the presence of sodium hydride, using THF as the solvent. In Step 2, the pyrrole and exocyclic double bonds are hydrogenated over platinum oxide in acetic acid. This is followed in Step 3 by partial reduction of the side-chain methyl ester group to an aldehyde moiety using DIBAL-H in THF at -80°C .

In a variant of the reaction scheme described immediately above, a chiral intermediate of formula VII, in which R^{21} represents a pyrrolidin-2-ylmethyl moiety having a chiral centre at the 2-position and protected on the ring nitrogen atom by a BOC group, is illustrated by the following reaction scheme:

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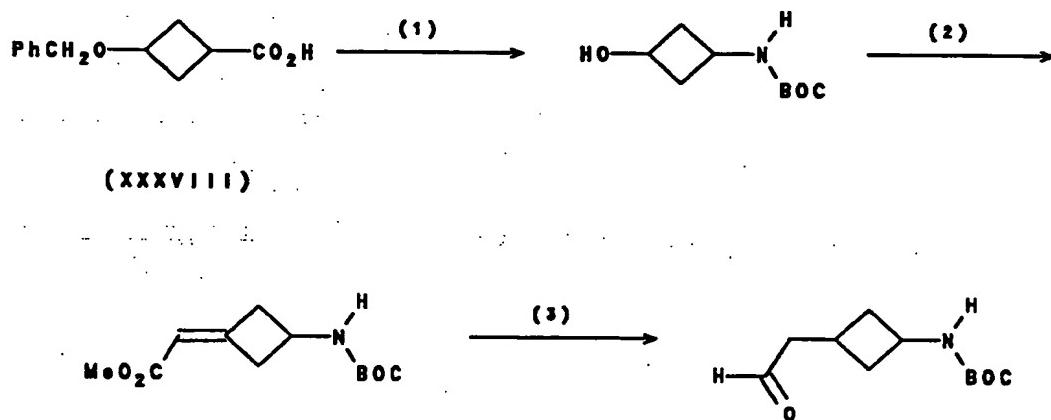


The starting compound XXXVI, D-prolinol, is commercially available from Aldrich Chemical Company Ltd., Gillingham, U.K. Step 1 of the reaction scheme involves protection of the pyrrolidine nitrogen as the N-BOC derivative, typically using BOC anhydride in dichloromethane; followed by Swern oxidation (oxalyl chloride/dimethyl sulphoxide/dichloromethane/-78°C, then triethylamine) of the terminal hydroxy group to an aldehyde moiety. Step 2 involves reaction with the Horner-Emmons reagent $\text{MeO}_2\text{C}.\text{CH}_2.\text{PO}(\text{OEt})_2$ in the presence of sodium hydride, using THF as the solvent. In Step 3 the side-chain double bond is reduced, conveniently by catalytic hydrogenation over palladium-charcoal in aqueous methanol; and the methyl ester moiety is then partially reduced to an aldehyde functionality using DIBAL-H in THF at -78°C, to give the desired product of formula XXXVII.

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As will be appreciated, the compound corresponding to compound XXXVII, but having the opposite stereochemistry at the 2-position of the pyrrolidine ring, is readily obtainable, using an identical sequence of steps, from L-prolinol (i.e. the opposite antipode of compound XXXVI), which is also commercially available from Aldrich Chemical Company Ltd.

The preparation of a still further typical intermediate of formula VII, in which R²¹ represents a BOC-protected 3-aminocyclobutan-1-yl moiety, is illustrated by the following reaction scheme:



The starting compound XXXVIII is known from Coll. Czech. Chem. Commun., 1981, 47, 2440. Step 1 of the reaction scheme involves treatment thereof with diphenylphosphoryl azide and 2-methyl-2-propanol in the presence of triethylamine under reflux, to convert the carboxylic acid moiety into an -NHBOC group; followed by removal of the O-benzyl protecting group by catalytic hydrogenation over palladium/carbon. In Step 2, the

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hydroxy group is oxidised to keto using pyridinium chlorochromate, or N-methylmorpholine N-oxide in the presence of tetrapropylammonium perruthenate and molecular sieve; and the resulting keto group is in turn 5 reacted with the Horner-Emmons reagent $\text{MeO}_2\text{C} \cdot \text{CH}_2 \cdot \text{PO(OEt)}_2$ in the presence of potassium bis(trimethylsilyl)amide. Step 3 comprises reduction of the exocyclic double bond, conveniently by catalytic hydrogenation over palladium on carbon; and then partial reduction of the side-chain 10 methyl ester group to an aldehyde moiety using DIBAL-H in toluene at about -80°C .

It will be understood that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be 15 elaborated into a further compound of formula I by techniques known from the art. Indeed, as will be appreciated, the compound of formula XV above in which R^d is a group of formula $-E-F$ is itself a compound of formula I in which A^1 is hydrogen and A^2 represents a non-bonded electron pair. In particular, a compound of 20 formula I wherein R^3 is hydrogen initially obtained may be converted into a compound of formula I wherein R^3 represents C₁₋₆ alkyl by standard alkylation techniques, for example by treatment with an alkyl iodide, e.g. 25 methyl iodide, typically under basic conditions, e.g. sodium hydride in dimethylformamide, or triethylamine in acetonitrile. Similarly, a compound of formula I wherein R^4 , R^5 or R^6 represents hydrogen initially obtained may be converted into a compound of formula I wherein R^4 , R^5 30 or R^6 is other than hydrogen, for example by conventional N-alkylation techniques, e.g. by treatment with the appropriate aldehyde in the presence of a reducing agent such as sodium cyanoborohydride.

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Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography.

The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

The ability of test compounds to bind to 5-HT₁-like receptors was measured in membranes prepared from pig caudate using the procedure described in J. Neurosci., 1987, 7, 894. Binding was determined using

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2 nM 5-hydroxytryptamine creatinine sulphate,
5-[1,2-³H(N)] as a radioligand. Cyanopindolol (100 nM)
and mesulergine (100 nM) were included in the assay to
block out 5-HT_{1A} and 5-HT_{1C} binding sites respectively.

5 The concentration of the compounds of the accompanying
Examples required to displace 50% of the specific binding
(IC₅₀) is below 1 μM in each case.

10 The activity of test compounds as agonists of
the 5-HT₁-like receptor was measured in terms of their
ability to mediate contraction of the saphenous vein of
New Zealand White rabbits, using the procedure described
in Arch. Pharm., 1990, 342, 111. Agonist potencies were
calculated as -log₁₀EC₅₀ (pEC₅₀) values, from plots of
percentage 5-HT (1 μM) response against the concentration
15 of the agonist. The compounds of the accompanying
Examples were found to possess pEC₅₀ values in this assay
of not less than 5.0 in each case.

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EXAMPLE 1

N-2-[5-(1,2,4-Triazol-1-ylmethyl)-1H-indol-3-yl]ethyl azetidine. Hydrogen Oxalate.

5

INTERMEDIATE 1

4-(1-Azetidinyl)butanal dimethylacetal

A mixture of azetidine (2.0g, 35.0mmol), 4-chlorobutanal dimethylacetal (5.88g, 39.0mmol) and K_2CO_3 (5.38g, 39.0mmol),
10 in anhydrous DMF (100ml), was stirred at room temperature for 72 h. Water (50ml) was added and the mixture extracted with EtOAc (3x150ml). The combined extracts were washed with H_2O (3x50ml), dried (Na_2SO_4) and evaporated. The crude product
15 was purified by distillation (1.2g). δ (360MHz, $CDCl_3$) 1.35-1.42 (2H, m, CH_2), 1.57-1.64 (2H, m, CH_2), 2.00-2.40 (2H, m, CH_2),
2.36 (2H, t, J = 9.0Hz, CH_2), 3.15 (4H, m, t, J = 7.0Hz, 2 of CH_2),
3.33 (6H, s, 2 of OMe), 4.35 (1H, t, J = 5.7Hz, CH).

20

INTERMEDIATE 2

1-(4-Hydrazinophenyl)methyl-1,2,4-triazole

1. 1-(4-Nitrophenyl)methyl-1,2,4-triazole

25

4-Nitrobenzylbromide (21.6g, 0.1mol) was added to a rapidly stirred suspension of 1,2,4-triazole sodium salt (9.1g, 0.1mol) in anhydrous DMF (100ml) and the mixture stirred at room temperature for 16h. Ethyl acetate (400ml) was added followed by water (250ml) and the layers separated. The organic phase was washed with water (3 x 250ml), dried ($MgSO_4$) and

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EXAMPLE 1

N-2-[5-(1,2,4-Triazol-1-ylmethyl)-1H-indol-3-yl]ethyl azetidine. Hydrogen Oxalate.

5

INTERMEDIATE 1

4-(1-Azetidinyl)butanal dimethylacetal

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15 was purified by distillation (1.2g). δ (360MHz, $CDCl_3$) 1.35-1.42 (2H, m, CH_2), 1.57-1.64 (2H, m, CH_2), 2.00-2.40 (2H, m, CH_2),
2.36 (2H, t, J = 9.0Hz, CH_2), 3.15 (4H, m, t, J = 7.0Hz, 2 of CH_2),
3.33 (6H, s, 2 of OMe), 4.35 (1H, t, J = 5.7Hz, CH).

20

INTERMEDIATE 2

1-(4-Hydrazinophenyl)methyl-1,2,4-triazole

1. 1-(4-Nitrophenyl)methyl-1,2,4-triazole

25

4-Nitrobenzylbromide (21.6g, 0.1mol) was added to a rapidly stirred suspension of 1,2,4-triazole sodium salt (9.1g, 0.1mol) in anhydrous DMF (100ml) and the mixture stirred at room temperature for 16h. Ethyl acetate (400ml) was added followed by water (250ml) and the layers separated. The organic phase was washed with water (3 x 250ml), dried ($MgSO_4$) and

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evaporated. The residue was chromatographed on silica gel eluting with ethyl acetate to give the title-product (10.6g, 52%); m.p. 98-100°C. δ (360MHz, CDCl₃) 5.47 (2H, s, CH₂), 7.40 (2H, d, J = 9Hz, Ar-H), 8.02 (1H, s, Ar-H), 8.18 (1H, s, Ar-H), 8.23 (2H, d, J = 9Hz, Ar-H).

5

2. 1-(4-Aminophenyl)methyl-1,2,4-triazole Hydrochloride

10

A solution of 1-(4-nitrophenyl)methyl-1,2,4-triazole (10.0g, 49mmol) in ethanol (50ml), ethyl acetate (50ml), 5N HCl (10ml) and water (10ml) was hydrogenated over 10% Pd/C(1.0g) at 40 psi, in a Parr apparatus, until an uptake of 188 psi, had been observed (approx 10mins). The catalyst was removed by filtration through hyflo and the solvent removed under vacuum.

15

The residue was azeotroped with ethanol (x2) to give the title-amine hydrochloride (10.6g, 100%). δ (360MHz, D₂O) 5.53 (2H, s, CH₂), 7.37-7.48 (4H, m, Ar-H), 8.12 (1H, s, Ar-H), 8.66 (1H, s, Ar-H).

20

3. 1-(4-Hydrazinophenyl)methyl-1,2,4-triazole

25

A solution of sodium nitrite (3.28g, 48mmol) in water (20ml) was added to a solution of the preceding amine hydrochloride (10.0g, 48mmol), in concentrated HCl (40ml), at such a rate that the temperature did not exceed -10°C: After addition was complete the solution was stirred at 0°C for 0.25h and then added portionwise to a rapidly stirred solution of SnCl₂.2H₂O (40g) in concentrated HCl (40ml). The solution was warmed to room temperature and basified with 20% aqueous NaOH solution. The solution was extracted with ethyl acetate (3 x 250ml) and the combined extracts dried (MgSO₄) and filtered through hyflo. The solution was evaporated to dryness to give the desired hydrazine (5.0g, 56%) m.p. 109-112°C. δ (360MHz,

30

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D₆-DMSO) 3.93 (2H, br s, NH₂), 5.20 (2H, s, CH₂), 6.73 (2H, d, J = 8Hz, Ar-H), 7.08 (2H, d, J = 8Hz, Ar-H), 7.92 (1H, s, Ar-H), 8.57 (1H, s, Ar-H).

5 N-2-[5-(1,2,4-Triazol-1-ylmethyl)-1H-indol-3-yl]ethylazetidine. Hydrogen Oxalate. Hemihydrate.

A solution of 1-(4-hydrazinophenyl)methyl-1,2,4-triazole (0.92g, 4.1mmol) and 4-(1-azetidinyl)butanal dimethylacetal (0.65g, 3.8mmol), in 4% H₂SO₄ (30ml), was refluxed for 4.5h. The solution was cooled to room temperature, basified with K₂CO₃ and extracted with EtOAc (4x100ml). The combined extracts were dried (Na₂SO₄) and evaporated and the residue chromatographed on silica-gel eluting with CH₂Cl₂/MeOH/NH₃ (40:8:1) to give the title-indole. The hydrogen oxalate hemihydrate salt was prepared (30mg); m.p. 128-129°C. Found: C, 57.28, H, 5.95; N, 18.05. C₁₆H₁₉N₅.C₂H₂O₄.0.45 H₂O requires C, 56.97; H, 5.82; N, 18.45%. δ (360MHz, D₂O) 2.30-2.54 (2H, m, CH₂), 3.07 (2H, t, J=7.0Hz, CH₂), 3.52 (2H, t, J=7.0Hz, CH₂), 3.94-4.13 (4H, m, 2 of CH₂), 5.51 (2H, s, CH₂), 7.20 (1H, dd, J=1.5 and 8.4 Hz, Ar-H), 7.30 (1H, s, Ar-H), 7.51 (1H, d, J=8.4Hz, Ar-H), 7.62 (1H, s, Ar-H), 8.05 (1H, s, Ar-H), 8.56 (1H, s, Ar-H).

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EXAMPLE 2

N-2-[5-(1,2,4-Triazol-1-yl)-1H-indol-3-yl]ethylazetidine.

Bisoxalate

INTERMEDIATE 3

5

4-(1,2,4-Triazol-1-yl)phenylhydrazine. Hydrochloride

1. 4-(1,2,4-Triazol-1-yl)nitrobenzene

1,2,4-Triazole sodium derivative (90%) (17.74g, 0.18mol)

10 and 1-fluoro-4-nitrobenzene (25g, 0.18mol), in DMF, (150ml) was stirred at room temperature for 4 days. Water (300ml) and ethyl acetate (500ml) were added and the mixture extracted. The organic layer was separated, washed with water (3 x 300 ml), dried ($MgSO_4$) and evaporated to give the desired product (24.8g); δ (360MHz, $CDCl_3$) 7.92 (2H, d, $J = 9.1Hz$, Ar-H); 8.17 (1H, s, Ar-H); 8.40 (2H, d, $J = 9.1Hz$, Ar-H); 8.48 (1H, s, Ar-H).

2. 4-(1,2,4-Triazol-1-yl)phenylhydrazine. Hydrochloride

20 Prepared from 4-(1,2,4-triazol-1-yl)nitrobenzene using the procedure described for the preparation of Intermediate 2. δ (360MHz, $CDCl_3$) 3.66 (2H, br s, NH_2), 5.36 (1H, br s, NH), 6.88-6.96 and 7.44-7.50 (both 2H, both m, Ar-H), 8.06 (1H, s, Ar-H), 8.42 (1H, s, Ar-H).

25 N-2-[5-(1,2,4-Triazol-1-yl)-1H-indol-3-yl]ethylazetidine.

Bisoxalate

30 A solution of 4-(1,2,4-triazol-1-yl)phenylhydrazine hydrochloride (0.85g, 4.0mmol) and 4-(1-azetidinyl)butanal dimethylacetal (0.63g, 3.6mmol), in 4% H_2SO_4 (30ml), was heated at reflux for 5h. The solution was cooled to room

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temperature, basified with saturated K_2CO_3 solution and extracted with EtOAc (4 x 70ml). The combined extracts were dried (Na_2SO_4) and evaporated and the crude product chromatographed on silica-gel eluting with $CH_2Cl_2/MeOH/NH_3$ (80:8:1) to give the title-product. The bisoxalate salt was prepared (0.16g), m.p. 164-165°C. Found: C, 48.26; H, 4.65, N, 14.09. $C_{15}H_{17}N_5.2.55(C_2H_2O_4)$ requires C, 48.58; H, 4.48; N, 14.09%. δ (360MHz, D_2O) 2.32-2.58 (2H, m, CH_2), 3.11 (2H, t, J = 7.0Hz, CH_2), 3.56 (2H, t, J = 7.0Hz, CH_2), 4.00-4.17 (2H, m, CH_2), 7.40 (1H, s, Ar-H), 7.49 (1H, dd, J = 2.0 and 8.7Hz, Ar-H), 7.64 (1H, d, J =8.7Hz, Ar-H), 7.90 (1H, d, J = 2.0Hz, Ar-H), 8.47 (1H, s, Ar-H), 9.18 (1H, s, Ar-H).

EXAMPLE 3

15 N-Methyl-3-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]methylazetidine, 0.65 Oxalate

INTERMEDIATE 4

20 N-tert-Butyloxycarbonyl-3-(2-formyl)ethylazetidine

1. N-Diphenylmethyldiazetidin-3-ol

25 Aminodiphenylmethane (100g, 0.54mol) was added to a solution of epichlorohydrin (50g, 0.54mol) in DMSO (135ml) and stirred at 25°C for 3 days. The solution was then heated at 70°C for 3 days before cooling to room temperature, adding 10% NaOH solution, and extracting with Et_2O (2 x 800ml). The combined extracts were washed with water (2 x 1l), dried (Na_2SO_4) and evaporated. The crude product was chromatographed on silica-gel eluting with $CH_2Cl_2/MeOH$ (98:2)

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to give the title-azetidinol (33.5g). δ (360MHz, CDCl₃) 2.30 (1H, br s, OH), 2.87-2.91 (2H, m, 2 of CH of CH₂), 3.51-3.55 (2H, m, 2 of CH of CH₂), 4.34 (1H, s, CH), 4.41-4.48 (1H, m, CH-OH), 7.13-7.39 (10H, m, Ar-H).

5

2. N-Diphenylmethylazetidin-3-one

Triethylamine (112.1g, 1.11mol) was added to a solution of N-diphenylmethylazetidin-3-ol (26.6g, 0.11mol) in DMSO (300ml). The solution was cooled to 10°C and a solution of sulphur trioxide-pyridine complex (112g, 0.7mol) in DMSO (500ml) added, rapidly. Stirring was continued at 10°C for 0.75h and the mixture then warmed to 25°C and stirred for 1h. The solution was poured into ice-water (2l) and extracted with EtOAc (3 x 1l). The combined extracts were washed with water (500ml) and brine (500ml) and dried (Na₂SO₄). The crude product was purified by chromatography through silica-gel eluting with petroleum ether/EtOAc (2:1) to give the desired ketone (25.8g), mp 74-75°C. δ (360MHz, CDCl₃) 4.00 (4H, s, 2 of CH₂), 4.59 (1H, s, CH), 7.19-7.49 (10H, m, Ar-H).

20

3. Methyl (1-diphenylmethylazetidin-3-ylidene)acetate

Methyl diethylphosphonoacetate (11.0g, 52.0mmol) in THF (10ml) was added dropwise to a stirred suspension of sodium hydride (2.1g, 60% dispersion in oil, 52.5mmol) in THF (40ml), at 10°C. The mixture was stirred for 0.6h and a solution of the preceding azetidinone (11.3g, 48.0mmol) in THF (50ml) then added dropwise at 10°C. The mixture was heated at 50°C for 3h before removing the solvent under vacuum and redissolving the residue in CH₂Cl₂ (200ml). The solution was washed with water (50ml) and sodium bisulphite solution (2 x 50ml) and dried (Na₂SO₄). Chromatography of the residue obtained, after removing the solvent, through silica-gel eluting with CH₂Cl₂/MeOH (98:2) gave the desired ester (13.1g), mp

- 49 -

83-84°C; δ (360MHz, CDCl₃) 3.65 (3H, s, CO₂Me), 3.88 (2H, m, 2 of CH of CH₂), 4.14-4.17 (2H, m, 2 of CH of CH₂), 4.52 (1H, s, CH), 5.65-5.68 (1H, m, vinyl-H), 7.17-7.44 (10H, m, Ar-H).

5 4. N-Diphenylmethyl-3-carbomethoxymethylazetidine
A mixture of the compound from step 3 (21.0g, 71.7mmol), Pd(OH)₂ (3.0g, 20% on C), methanol (500ml) and 2N HCl (37ml) was hydrogenated on a Parr shake apparatus for 2h. The catalyst was removed by filtration through celite and the solvents removed under vacuum. Saturated K₂CO₃ solution was added (50ml) and extracted with CH₂Cl₂ (2 x 250ml). The combined extracts were washed with H₂O (250ml) and brine (100ml), dried (Na₂SO₄) and evaporated to give the title-product as a pale yellow oil (19.3g). δ (360MHz, CDCl₃) 2.58 (2H, d, J = 7.3Hz, CH₂), 2.75-2.81 (3H, m, 2 of CH of CH₂ and CH), 3.35-3.38 (2H, m, 2 of CH of CH₂), 3.62 (3H, s, CO₂Me), 4.31 (1H, s, CH), 7.14-7.18, 7.23-7.27 and 7.38-7.40 (total 10H, each m, Ar-H).

20 5. Ethyl-2-(1-diphenylmethylazetidin-3-yl)alcohol
Diisobutylaluminium hydride (119ml of a 1M solution in toluene, 0.119mol) was added dropwise to a stirred solution of the preceding ester (10.0g, 33.9mmol) in toluene (500ml), at -35°C, over a 0.5h period. The solution was warmed to 25°C, stirred for 2h, and then cooled to 0°C and quenched by addition of methanol (10ml), 2N NaOH (5ml) and H₂O (5ml). The mixture was warmed to 25°C, filtered through celite and the solvent removed under vacuum. The residue was chromatographed on silica-gel eluting with ethyl acetate/hexane (1:1) to give the title-alcohol as a white crystalline solid, (4.1g), mp 98-99°C.
25 Found: C, 80.73; H, 8.06; N, 5.38. C₁₈H₂₁NO requires C, 80.86; H, 7.92; N, 5.24%. δ (360MHz, CDCl₃) 1.64 (1H, br s, OH), 1.82 (2H, m, CH₂), 2.51-2.58 (1H, m, CH), 2.87-2.91 and 3.29-3.33
30

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(both 2H, each m, 2 of CH₂), 3.70 (2H, t, J = 6.4Hz, CH₂), 4.33 (1H, s, CH), 7.15-7.40 (10H, m, Ar-H).

6. Ethyl-2-(1-H-azetidin-3-yl)alcohol. Hydrochloride

5 Pd(OH)₂ (0.8g, 20% on C) was added to a solution of the preceding alcohol (4.0g, 15.0mmol) in methanol (200ml) and 1N HCl (10ml), and the mixture hydrogenated on a Parr shake apparatus for 24h, at 55 psi. The mixture was filtered through celite and the solvent removed under vacuum. Diphenyl
10 methane was removed by triturating the residue with ether and decanting. The remaining product was dried under vacuum to give the desired product (2.0g); δ (250MHz, D₂O) 1.86-1.94 (2H, m, CH₂), 2.98-3.16 (1H, m, CH), 3.60 (2H, t, J = 6.4Hz, CH₂), 3.86-3.96 and 4.14-4.22 (both 2H, both m, 2 of CH₂).

15 7. Ethyl-2-(1-tert-butyloxycarbonylazetidin-3-yl)alcohol
A mixture of the product from step 6 (1.44g, 10.5mmol), triethylamine (3.21ml, 22.9mmol) and (BOC)₂O (3.43g, 15.7mmol), in THF (90ml) was stirred at 25°C for 2 days. The
20 solvent was removed under vacuum, water (70ml) added and extracted with EtOAc (3 x). The combined extracts were dried (MgSO₄), evaporated and the residue chromatographed on silica-gel eluting with CH₂Cl₂/MeOH (95:5) to give the title-product (2.12g). δ (250MHz, CDCl₃) 1.42 (9H, s, 3 of CH₃), 1.56 (1H, s, OH), 1.82-1.90 (2H, m, CH₂), 2.56-2.76 (1H, m, CH), 25 3.58-3.67 (4H, m, CH₂ and 2 of CH of CH₂), 4.00-4.06 (2H, m, 2 of CH of CH₂).

30 8. Ethyl-2-(1-tert-butyloxycarbonylazetidin-3-yl)p-toluenesulphonate

A solution of p-toluenesulphonyl chloride (1.57g, 8.2mmol) in CH₂Cl₂ (20ml) was added to a solution of the preceding alcohol (1.5g, 7.46mmol) and triethylamine (8.2mmol) in CH₂Cl₂ (130ml)

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at 0°C. A catalytic amount of DMAP was added and the mixture warmed to +25°C and stirred for 16h. The residue remaining after removal of solvent under vacuum was chromatographed on silica-gel eluting with CH₂Cl₂/MeOH (99:1) to give the desired tosylate (1.7g, 71%). δ (360MHz, CDCl₃) 1.42 (9H, s, 3 of CH₃), 1.91-1.97 (2H, m, CH₂), 2.46 (3H, s, CH₃), 2.53-2.61 (1H, m, CH), 3.51 (2H, dd, J=5.5 and 8.6Hz, 2 of CH of CH₂), 3.95 (2H, dd, J = 8.5 and 8.6Hz, 2 of CH of CH₂), 4.01 (2H, t, J = 6.1Hz, CH₂-OTs), 7.36 (2H, d, J = 8.1Hz, Ar-H), 7.78 (2H, d, J = 8.1Hz, Ar-H).

10

9. Ethyl-2-(1-tert-butyloxycarbonylazetidin-3-yl)nitrile

NaCN (0.35g, 7.1mmol) was added to a solution of the preceding tosylate (1.7g) in anhydrous DMSO (40ml) and the mixture stirred at 60°C for 16h. Saturated NH₄Cl solution (30ml) was added and the mixture extracted with CH₂Cl₂ (300ml). The CH₂Cl₂ extract was washed with H₂O (4 x), dried (Na₂SO₄) and evaporated. The crude product was purified by chromatography on silica-gel eluting with CH₂Cl₂/MeOH (98:2). The product was obtained as a clear oil (0.92g, 92%); δ (360MHz, CDCl₃) 1.44 (9H, s, 3 of CH₃), 1.94-2.00 (2H, m, CH₂), 2.34 (2H, t, J = 7.1Hz, CH₂CN), 2.61-2.69 (1H, m, CH), 3.59 (2H, dd, J = 5.4 and 8.7Hz, 2 of CH of CH₂), 4.07 (2H, dd, J = 8.4 and 8.7Hz, 2 of CH of CH₂).

25

10. N-tert-Butyloxycarbonyl-3-(2-formyl)ethylazetidine

Diisobutylaluminium hydride (6.43ml of a 1M solution in toluene, 6.4mmol) was added to a solution of the preceding nitrile (0.9g, 4.3mmol) in toluene (100ml), at -60°C. The solution was warmed to +25°C and stirred for 5h before adding saturated NH₄Cl solution (50ml) and stirring for 16h. The mixture was extracted with CH₂Cl₂ (3 x), the combined extracts dried (Na₂SO₄) and the residue remaining, after removal of solvents under reduced pressure, chromatographed on silica gel, eluting

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with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (98:2) to give the title-aldehyde (0.42g, 46%);
δ (250MHz, CDCl_3) 1.44 (9H, s, 3 of CH_3), 1.86-1.96 (2H, m,
 CH_2), 2.40-2.60 (3H, m, CH and CH_2), 3.53 (2H, dd, $J = 5.4$ and
8.7Hz, 2 of CH of CH_2), 4.00 (2H, dd, $J = 8.5$ and 8.6Hz, 2 of CH
5 of CH_2).

N-H-3-[5-(1,2,4-Triazol-1-ylmethyl)-1H-indol-3-yl]methylazetidine

A mixture of the preceding aldehyde (0.4g, 1.88mmol) and
10 1-(4-hydrazinophenyl)methyl-1,2,4-triazole hydrochloride (0.51g,
2.26mmol) in 4% H_2SO_4 was heated at reflux for 3h. The
solution was cooled to 0°C, basified (K_2CO_3) and extracted with
 EtOAc (3 x). The combined extracts were dried (MgSO_4),
evaporated, and the residue purified by chromatography on
15 silica-gel eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3$ (15:8:1). The product
(0.16g, 34%) was obtained as a colourless foam; δ (360MHz,
 $\text{D}_4\text{-MeOH}$) 2.94 (2H, d, $J = 7.6\text{Hz}$, CH_2), 3.04-3.16 (1H, m, CH),
3.46-3.54 and 3.68-3.74 (both 2H, each m, 2 of CH_2), 5.36 (2H, s,
 CH_2), 7.02 (1H, s, Ar-H), 7.03 (1H, dd, $J = 1.5$ and 8.4Hz, Ar-H),
20 7.25 (1H, d, $J = 8.4\text{Hz}$, Ar-H), 7.48 (1H, s, Ar-H), 7.87 (1H, s,
Ar-H), 8.35 (1H, s, Ar-H).

**N-Methyl-3-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]
methylazetidine. 0.65 Oxalate**

25 To a cooled solution of the preceding 1H-azetidine (0.16g,
0.60mmol), NaCNBH_3 (45mg, 0.72mmol) and acetic acid
(90.0mg, 1.5mmol), in methanol (12ml), was added a solution of
formaldehyde (57.0mg, 0.72mmol; 38% w/v) in methanol (13ml),
30 at such a rate as to keep the temperature of the solution at 0°C.
The mixture was stirred at 0°C for 0.25h and then warmed to
room temperature and stirred for 1h. Saturated K_2CO_3 solution
(15ml) was added and the solvent removed under vacuum. The

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aqueous was extracted with EtOAc (4 x), the combined extracts dried ($MgSO_4$) and the solvent evaporated. The crude product was chromatographed on silica-gel eluting with $CH_2Cl_2/EtOH/NH_3$ (70:8:1) to give the title-product (0.12g, 71%).

5 The 0.65 oxalate salt was prepared, mp 209-210°C. Found: C, 61.31; H, 6.21; N, 20.23. $C_{16}H_{19}N_5$. 0.65 ($C_2H_2O_4$) requires C, 61.14; H, 6.02; N, 20.61%); δ (360MHz, D_2O) 2.75 and 2.91 (total 3H, each s, N- CH_3), 3.04 and 3.09 (total 2H, each d, J = 7.7Hz, CH_2), 3.26-3.37 (1H, m, CH), 3.77 and 3.98 (total 2H, each dd, J =9.0 and 11.0Hz, 2 of CH of CH_2), 4.14 and 4.32 (total 2H, each dd, J = 6.3 and 11.0Hz, 2 of CH of CH_2), 5.12 (2H, s, CH_2), 7.21 (1H, d, J = 8.4Hz, Ar-H), 7.28 (1H, s, Ar-H), 7.51 (1H, dd, J = 1.5 and 8.4Hz, Ar-H), 7.60 and 7.63 (total 1H, each s, Ar-H), 8.05 (1H, s, Ar-H), 8.54 (1H, s, Ar-H).

15

EXAMPLE 4

(±)-N-Methyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]methylpyrrolidine. Hydrogen Oxalate. 0.2 Hydrate

20

INTERMEDIATE 5

(±)-N-tert-Butyloxycarbonyl-2-(2-formyl)ethyl pyrrolidine

25

1. N-tert-Butyloxycarbonylpvrrole-2-carboxaldehyde

A mixture of pyrrole-2-carboxaldehyde (9.5g, 0.1mol), $(BOC)_2O$ (24.0g, 0.11mol) and DMAP (0.25g) in THF (150ml) was stirred at room temperature for 16h. The solvent was removed under vacuum and the residue dissolved in CH_2Cl_2 (200ml) and washed with 10% citric acid, water and brine. The organic layer was dried (Na_2SO_4) and evaporated to give the

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desired product (20.9g, 95%); δ (360MHz, CDCl₃) 1.65 (9H, s, 3 of CH₃), 6.28-6.30 (1H, m, Ar-H), 7.18-7.19 (1H, m, Ar-H), 7.43-7.45 (1H, m, Ar-H).

5 2. trans-Methyl-2-(N-tert-butyloxycarbonylpyrrol-2-yl)acrylate

Prepared from the preceding aldehyde and methyl diethylphosphonoacetate as described for Intermediate 4 (step 3). The product (98%) was obtained as a pale yellow oil; δ (360MHz, CDCl₃) 1.63 (9H, s, 3 of CH₃), 3.78 (3H, s, CH₃), 6.21 (1H, d, J=16.0Hz, vinyl CH), 6.21-6.22 (1H, m, Ar-H), 6.69-6.71 (1H, m, Ar-H), 7.38-7.39 (1H, m, Ar-H), 8.30 (1H, d, J=16.0Hz, vinyl CH).

10 3. (±)-Methyl-2-(N-tert-butyloxycarbonylpyrrolidin-2-yl)propionate

15 A solution of the product from step 2 (11.0g, 43.8mmol) in glacial AcOH (300ml) was hydrogenated over PtO₂ (1.25g) at 50psi. The catalyst was removed by filtration through hyflo and the solvent removed under vacuum. The crude product was chromatographed on silica-gel eluting with diethyl ether:petroleum ether (1:1) to give the title-ester (7.4g, 67%); δ (360MHz, CDCl₃) 1.46 (9H, s, 3 of CH₃), 1.53-2.07 (6H, m, 3 of CH₂), 2.24-2.40 (2H, m, CH₂), 3.25-3.46 (2H, m, CH₂), 3.67 (3H, s, CO₂CH₃), 3.61-3.66 (1H, m, CH).

20 4. (±)-N-tert-Butyloxycarbonyl-2-(2-formyl)ethylpyrrolidine

25 To a cooled (-78°C) solution of the preceding ester (4.0g, 15.56mmol) in anhydrous toluene (75ml) was added dropwise a solution of diisobutylaluminium hydride (18.7ml of a 1M solution in toluene, 18.7mmol), at such a rate as to maintain the temperature below -75°C. After the addition was complete the reaction was stirred at -78°C for 4h before adding MeOH (1ml), H₂O (1ml) and sodium hydroxide (2N, 1ml), successively,

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dropwise. The mixture was warmed to room temperature and the precipitated salts removed by filtration through hyflo. The filtrate was dried ($MgSO_4$) and the solvent removed under vacuum. The residue was chromatographed on silica-gel eluting with ethyl acetate/petroleum ether (3:4) to give the title-compound (2.74g, 78%) as a colourless oil; δ (360MHz, $CDCl_3$) 1.46 (9H, s, 3 of CH_3), 1.58-1.99 (6H, m, 3 of CH_2), 2.45 (2H, d t, J = 1.2 and 7.5Hz, CH_2 -CHO), 3.25-3.39 (2H, m, CH_2), 3.78-3.88 (1H, m, CH), 9.76 (1H, t, J = 1.2Hz, CHO).

10

(\pm)-N-Methyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]methylpyrrolidine. Hydrogen Oxalate. 0.2 Hydrate

15

Prepared from (\pm N-*tert*-butyloxycarbonyl-2-(2-formyl)ethylpyrrolidine and 1-(4-hydrazinophenyl)methyl-1,2,4-triazole hydrochloride as described for Example 3. The hydrogen oxalate salt was prepared, mp 161-162°C (MeOH/ether). Found: C, 57.97; H, 5.82; N, 17.53. $C_{17}H_{21}N_5$. $C_2H_2O_4 \cdot 0.2H_2O$ requires C, 57.94; H, 5.98; N, 17.53%); δ (360MHz, D_2O) 1.81-2.25 (4H, m, CH_2), 2.84 (3H, s, CH_3), 3.08-3.18, 3.29-3.35 and 3.65-3.74 (2H, 1H, and 2H respectively, each m, 2 of CH_2 and CH), 5.52 (2H, s, CH_2), 7.22 (1H, d, J = 8.4Hz, Ar-H), 7.36 (1H, s, Ar-H), 7.53 (1H, d, J = 8.4Hz, Ar-H), 7.63 (1H, s, Ar-H), 8.08 (1H, s, Ar-H), 8.59 (1H, s, Ar-H).

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EXAMPLE 5

(2R)-N-Methyl-2-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]methylpyrrolidine. 1.3 Benzoate. 0.9 Hydrate

5

INTERMEDIATE 6

4'-(1,2,4-Triazol-4-yl)phenylhydrazine

1. 4'-Aminoacetanilide

10 A solution of 4-nitroacetanilide (5.0g, 27.8mmol) in EtOH/EtOAc (160ml, 1:1), H₂O (15ml) and 5N HCl (5.6ml, 28.0mmol) was hydrogenated over 10% Pd-C (0.50g) at 50 psi for 0.25h. The catalyst was removed by filtration through celite and the solvents removed under vacuum. The free base was
15 generated by dissolving the product in H₂O, basifying with 2N NaOH and extracting into EtOAc. The combined extracts were dried (MgSO₄) and evaporated to give the title-aniline (3.75g, 90%). δ (250MHz, CDCl₃/d₄-MeOH) 2.10 (3H, s, CH₃), 6.68 (2H, d, J = 8.8Hz, Ar-H), 7.27 (2H, d, J = 8.8Hz, Ar-H).

20

2. 4'-(1,2,4-Triazol-4-yl)acetanilide

25 A mixture of the preceding aniline (3.52g, 23.4mmol), N,N-dimethylformamide azine (3.33g, 23.4mmol; J. Chem. Soc. (C) 1967, 1664) and p-toluenesulphonic acid monohydrate (0.223g, 1.17mmol), in anhydrous toluene (100ml), was heated at reflux for 17h. The beige coloured precipitate was filtered off and washed with toluene and CH₂Cl₂ and dried under vacuum to give the desired triazole (4.29g, 91%); δ (250MHz, d₄-MeOH/d₆-DMSO) 2.14 (3H, s, CH₃), 7.60 (2H, d, J = 8.8Hz, Ar-H), 7.78 (2H, d, J = 8.8Hz, Ar-H), 8.96 (2H, s, Ar-H).

30

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3. 4'-(1,2,4-Triazol-4-yl)phenylaniline

A solution of the preceding acetanilide (4.91g, 24.3mmol) in 5N HCl (100ml) was heated at 125°C for 1.5h. The mixture
5 was cooled to 0°C, basified with concentrated aqueous NaOH solution and extracted with CH₂Cl₂ (x 5). The combined extracts were dried (MgSO₄) and evaporated and the residue chromatographed on silica gel, eluting with CH₂Cl₂/MeOH/NH₃ (80:8:1), to give the title-aniline (2.94g, 76%); δ (250MHz, CDCl₃)
10 3.80 (2H, s, NH₂), 6.71 (2H, d, J = 8.8Hz, Ar-H), 7.08 (2H, d, J = 8.8Hz, Ar-H), 8.36 (2H, s, Ar-H).

4. 4'-(1,2,4-Triazol-4-yl)phenylhydrazine

15 To a solution of the preceding aniline (1.60g, 9.99mmol) in concentrated HCl/H₂O (23ml and 3ml respectively) was added, at -21°C, a solution of NaNO₂ (0.69g, 9.99mmol) in H₂O (8ml), at such a rate as to maintain the temperature below -10°C. The mixture was stirred for 0.3h and then filtered rapidly through a
20 sinter, under vacuum. The filtrate was added to a cooled (-20°C) solution of SnCl₂.2H₂O (9.02g, 40.0mmol) in concentrated HCl (17ml). The mixture was stirred at -20°C for 0.25h and then at room temperature for 1.25h. The resulting solid was filtered off, washed with Et₂O and dried under vacuum. The crude product
25 was dissolved in H₂O, basified with concentrated aqueous NaOH and extracted with EtOAc (x 5). The combined extracts were dried (MgSO₄) and evaporated to afford the title-product (0.95g, 54%); δ (250 MHz, CDCl₃/d₄-MeOH) 3.98 (3H, br s, NH and NH₂); 6.97 (2H, d, J = 12.0Hz, Ar-H); 7.25 (2H, d, J = 12.0Hz,
30 Ar-H); 8.48 (2H, s, Ar-H).

INTERMEDIATE 7(2R)-N-tert-Butyloxycarbonyl-3-(pyrrolidin-2-yl)propanal5 1. (2R)-N-tert-Butyloxycarbonylpvrrolidin-2-ylmethanol

A solution of di-*tert*-butyl dicarbonate (34.11g, 156.3mmol) in DCM (125ml) was added dropwise to a stirred solution of D-prolinol (15.04g, 148.7mmol) in CH₂Cl₂ (125ml) at 0°C under nitrogen. The mixture was stirred at 0°C for 1h and then at room temperature for 66h. Evaporation of the solvent afforded the title-carbamate (29.9g, 100%); δ (360MHz, CDCl₃) 1.47 (9H, s, ^tBu), 1.60 (1H, br m, CH₂), 1.72-1.89 (2H, m, CH₂), 2.00 (1H, m, CH₂), 3.31 (1H, m, CH₂), 3.46 (1H, m, CH₂), 3.55-3.66 (2H, m, CH₂), 3.95 (1H, br m, CH₂).

10 2. (2R)-N-tert-Butyloxycarbonylpvrrolidin -2-ylmethanol

DMSO (8.63ml, 122mmol) was added dropwise to a stirred solution of oxalyl chloride (5.31ml, 60.9mmol) in CH₂Cl₂ (350ml) at -78°C under nitrogen. The mixture was stirred at this temperature for 30mins before adding a solution of the preceding alcohol (10.20g, 50.68mmol) in CH₂Cl₂ (120ml). After stirring at -78°C for 95mins, triethylamine (35.5ml, 255mmol) was added dropwise and the mixture allowed to warm to room temperature. Water was added, the mixture extracted with CH₂Cl₂ and the combined extracts dried (MgSO₄) and evaporated. The residue was purified by flash chromatography on silica gel, eluting with 1:1 ethyl acetate/hexane, to afford the title-aldehyde (10.1g, 100%); δ (360MHz, CDCl₃) 1.38 and 1.41 (9H, 2 x s, ^tBu), 1.79-2.06 (4H, m, CH₂), 3.39-3.48 (2H, m, CH₂), 3.98 and 4.14 (1H, 2 x m, CH₂), 9.40 and 9.49 (1H, 2 x s, CHO).

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3. (2R)-trans-Methyl [N-tert-butyloxycarbonyl-3-(pyrrolidin-2-yl)]propenoate

Methyl diethylphosphonoacetate (3.71, 20.2mmol) was
5 added dropwise to a stirred suspension of sodium hydride (0.81g,
60% dispersion in oil, 20.3mmol) in THF (30ml) at 4°C under
nitrogen. The mixture was stirred at room temperature for 0.5h,
recooled to 2°C and a solution of the preceding aldehyde (4.03g,
20.2mmol) in THF (35ml) added dropwise, maintaining the
10 temperature below 10°C. The mixture was stirred at 7.5°C for
2.5h before evaporating the solvent *in vacuo* and redissolving the
residue in CH₂Cl₂. The solution was washed with water (x1),
20% w/v sodium bisulphite solution (x2) and water (x1), dried
(MgSO₄) and evaporated. Flash chromatography on silica gel of
15 the residue, eluting with 40:60 ethyl acetate/hexane, afforded
the title - ester (4.92g, 95%); δ (360MHz, CDCl₃) 1.42 (9H, br s,
^tBu), 1.78-1.88 (3H, m, CH₂), 2.08 (1H, m, CH₂), 3.44 (2H, br s,
CH₂), 3.74 (3H, s, CO₂Me), 4.37-4.50 (1H, m, CH), 5.83 (1H, d,
J=15.2Hz, vinyl CH), 6.83 (1H, m, vinyl CH).

20 4. (2R)-Methyl [N-tert-butyloxycarbonyl-3-(pyrrolidin-2-yl)
propanoate

A mixture of the preceding olefinic ester (4.34g, 17.0mmol)
25 10% Pd/C (0.43g), methanol (30ml) and water (10ml) was
hydrogenated on a Parr shake apparatus for 2h. The catalyst
was removed by filtration through celite and the solvents
evaporated *in vacuo*. Flash chromatography of the residue on
silica gel, eluting with 30:70 ethyl acetate/hexane, afforded the
30 title - ester (4.21g, 96%); [α]_D + 36.5° (c 0.37, CH₂Cl₂);
δ (360MHz, CDCl₃) 1.46 (9H, s, ^tBu), 1.54-2.02 (6H, m, CH₂),
2.33 (2H, t, J=7.8Hz, m, CH₂), 3.29 (1H, m, CH₂), 3.39 (1H, m,
CH₂), 3.67 (3H, s, CO₂Me), 3.81 (1H, m, CH).

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5. (2R)-N-tert-Butyloxycarbonyl-3-(pyrrolidin-2-yl)propanal

Prepared from the preceding ester using the procedure
described for the preparation of Intermediate 5 (step 4). δ
(250MHz, CDCl₃) 1.46 (9H, s, ^tBu), 1.58-1.99 (6H, m, CH₂), 2.45
(2H, dt, J=1.2 and 7.5Hz, CH₂-CHO), 3.25-3.39 (2H, m, CH₂),
3.83 (1H, m, CH), 9.76 (1H, t, J=1.2Hz, CHO).

10 (2R)-2-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]methylpyrrolidine

A solution of 4'-(1,2,4-triazol-4-yl)phenylhydrazine dihydrochloride (1.12g, 4.49mmol) and (2R)-N-*tert*-butyloxycarbonyl-3-(pyrrolidin-2-yl)propanal (0.847g, 3.73mmol) in
15 4% aqueous sulphuric acid (80ml) was stirred at room temperature for 0.5h and then heated at reflux for 25h. After cooling to room temperature, n-butanol was added and the aqueous basified with saturated aqueous potassium carbonate solution. The aqueous was separated and extracted further with n-butanol (x2). The combined
20 organics were evaporated *in vacuo* and the residue flash chromatographed on silica gel eluting with CH₂Cl₂/MeOH/NH₃ (20:8:1), to give the title - pyrrolidine (0.263g, 26%); δ (360MHz,
d⁴-MeOH) 1.47 (1H, m, CH₂), 1.68-1.94 (3H, m, CH₂), 2.61 (1H, m,
CH₂), 2.92 (2H, d, J=6.8Hz, CH₂), 3.01 (1H, m, CH₂), 3.42 (1H,
25 pentet, J=7.4Hz, CH), 7.19-7.22 (2H, m, Ar-H), 7.43 (1H, d,
J=8.7Hz, Ar-H), 7.71 (1H, d, J=1.8Hz, Ar-H), 8.82 (2H, s, Ar-H).

30 (2R)-N-Methyl-2-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]
methylpyrrolidine. 1.3 Benzoate. 0.9 Hydrate.

Prepared from the preceding pyrrolidine using the procedure described for Example 3. The benzoate salt was prepared; (Found: C, 66.13; H, 6.34; N, 15.19.

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$C_{16}H_{19}N_5 \cdot 1.3(C_7H_6O_2)$. 0.9(H_2O) requires C, 66.06; H, 6.32; N, 15.35%; δ (360MHz, D_2O) 1.86-2.09 (3H, m, CH_2), 2.27 (1H, m, CH_2), 2.86 (3H, s, CH_3), 3.13-3.21 (2H, m, CH_2), 3.38 (1H, dd, J=14.8 and 6.0Hz, CH_2), 3.68-3.76 (2H, m, CH_2), 7.34 (1H, dd, J=8.6 and 2.0Hz, Ar-H), 7.46-7.60 (5H, m, Ar-H), 7.65 (1H, d, J=9.0Hz, Ar-H), 7.76 (1H, d, J=2.0Hz, Ar-H), 7.88-7.91 (2.5H, m, Ar-H), 8.82 (2H, s, Ar-H).

EXAMPLE 6

10

3-[trans-1-(Dimethylamino)cyclobutan-3-yl]-5-[(1,2,4-triazol-1-yl)methyl]-1H-indole and 3-[cis-1-(Dimethylamino)cyclobutan-3-yl]-5-[(1,2,4-triazol-1-yl)methyl]-1H-indole. Hydrogen Oxalates.

15

1. cis/trans-1-Benzylxy-3-(tert-butyloxycarbonyl amino)cyclobutane

20

To a stirred solution of *cis/trans*-3-benzylxycyclobutane-1-carboxylic acid (5.0g, 24.24mmol) (Coll. Czech. Chem. Commun., 1981, 47, 2440) in anhydrous 2-methyl-2-propanol (70ml) was added anhydrous triethylamine (3.72ml, 26.67mmol) followed by diphenylphosphoryl azide (5.48ml, 25.45mmol) and the resulting colourless clear solution was refluxed for 19 hours under a nitrogen atmosphere. Solvents were removed under vacuum and the remaining liquid was dissolved in ethyl acetate (200ml) and it was washed with 1N hydrochloric acid (1 x 50ml), water (1 x 50ml), 10% aqueous sodium bicarbonate (1 x 50ml), brine (1 x 20ml), then dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (silica gel, hexane-ethyl acetate, 85:15 to 70:30) gave 3.30g of the title compound (*cis/trans* 1:1) as a white solid; δ (250MHz, $CDCl_3$) 7.38-7.25 (5H, m, Ph-), 4.63

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(1H, br s, -NH-), 4.40 (2H, s, PhCH₂-), 4.26-4.12 (1H, m, -CH-O),
3.75 (1H, qn, J = 7.5Hz, -CH-N), 2.78-2.64 (1H, m, -CH₂-),
2.50-2.36 (1H, m, -CH₂-), 2.20-2.06 (1H, m, -CH₂-), 1.88-1.74 (1H,
m, -CH₂-), 1.44 (9H, s, t-Bu); m/z (CI) 276 (M⁺ -1).

5

2. cis/trans-3-(tert-Butyloxycarbonyl amino)cyclobutan-1-ol

A solution of *cis/trans-1-benzyloxy-3-(tert-butyloxycarbonylamino)* cyclobutane (3.0g) in absolute ethanol (40ml) was hydrogenated at 20 psi over 10% palladium on carbon (540mg) for 2 hours. The catalyst was removed by filtration, washed with ethanol (2 x 20ml) and the filtrate was concentrated under vacuum to give 2.05g (100%) of the title compound (*cis/trans*, 1:1) as a waxy white solid; mp 64-67°C (hexane-ethyl acetate); δ (250MHz, CDCl₃) 4.64 (2H, br s, -NH-), 4.54-4.42 (1H, m, -CH-), 4.28-4.14 (1H, m, -CH-), 4.02 (1H, qn, J = 7.3Hz, -CH-), 3.74-3.56 (1H, m, -CH-), 2.84-2.70 (2H, m, -CH₂-), 2.40-2.14 (4H, m, -CH₂), 1.88-1.70 (4H, m, -CH₂- and -OH), 1.43 (18H, s, t-Bu); m/z (CI) 187 (M⁺). (Found: C, 58.02; H, 9.02; N, 7.25. C₉H₁₇NO₃ requires: C, 57.73; H, 9.15; N, 7.48%).

3. 3-(tert-Butyloxycarbonylamino)cyclobutan-1-one

To a stirred solution of the product from the previous step (500mg, 2.67mmol) and N-methylmorpholine N-oxide monohydrate (541mg, 4.0mmol) in anhydrous dichloromethane (27ml) were added 4Å molecular sieves (500mg) and the mixture was stirred for 15 minutes prior to the addition of tetrapropylammonium perruthenate (47mg, 0.13mmol). After being stirred for 1.5 hours under a nitrogen atmosphere, the mixture was diluted with dichloromethane (100ml) and it was washed with 10% aqueous sodium sulphite (1 x 25ml), brine (1 x 25ml) and saturated aqueous copper (II) sulphate (1 x 25ml).

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The organic solution was filtered through a plug of flash silica gel (40g) and this was washed with ethyl acetate (3 x 20ml). The filtrate was concentrated under vacuum and the remaining residue was purified by flash chromatography (silica gel, 5 hexane-ethyl acetate, 60:40) to give 410mg (83%) of the title compound as a white solid; mp 75-78°C; δ (360MHz, CDCl₃) 4.90 (1H, br s, -NH-), 4.32-4.22 (1H, m, -CH-), 3.46-3.34 (2H, m, -CH₂-), 3.08-2.98 (2H, m, -CH₂-), 1.46 (9H, s, t-Bu); m/z (CI) 186 (M⁺ +1). (Found: C, 58.31; H, 7.96; N, 7.59. C₉H₁₅NO₃ requires: 10 C, 58.36; H, 8.16; N, 7.56%).

4. 1-(tert-Butyloxycarbonylamino)-3-(carbomethoxymethylene)cyclobutane

15 To a cooled (-70°C) and stirred solution of trimethyl phosphonoacetate (1.5g) in anhydrous tetrahydrofuran (40ml) was added potassium bis(trimethylsilyl)amide (0.5M in toluene; 15.07ml) at such a rate as to maintain the internal temperature below -62°C (ca 8 min). After 15 minutes of stirring at -70°C, a 20 solution of 3-(*tert*-butyloxycarbonylamino)cyclobutan-1-one (1.27g) in anhydrous tetrahydrofuran (10ml) was added over 9 minutes, under a nitrogen atmosphere. The mixture was then allowed to warm to room temperature and it was stirred for 1 hour before it was quenched with saturated aqueous ammonium 25 chloride (40ml). Products were extracted with ethyl acetate (2 x 50ml) and the combined organic solutions were washed with brine (1 x 40ml), dried (MgSO₄) and concentrated. Flash chromatography of the residue (silica gel, hexane-ethyl acetate, 75:25) gave 1.61g (97%) the title compound as a white solid; mp 79-82°C δ (250MHz, CDCl₃) 5.70 (1H, m, -CH-), 4.81 (1H, br s, -NH-), 4.32-4.13 (1H, m, -CH-), 3.69 (3H, s, -OMe), 3.64-3.50 (1H, m, -CH₂-), 3.26-3.10 (1H, m, -CH₂-), 3.00-2.86 (1H, m, -CH₂-), 2.80-2.68 (1H, m, -CH₂-), 1.45 (9H, s, t-Bu); m/z (CI) 240 (M⁺ -1).

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(Found: C, 60.28; H, 7.87; N, 5.76. $C_{12}H_{19}NO_4 \times 0.03 C_6H_{14}$
requires: C, 59.99; H, 8.02; N, 5.75%).

5 5. cis/trans-1-(tert-Butyloxycarbonylamino)-3-(carbomethoxymethyl)cyclobutane

A solution of the product from the previous step (1.5g) in
absolute ethanol (40ml) was hydrogenated at atmospheric
pressure over 10% palladium on carbon (200mg) for 2 hours.
10 The catalyst was filtered off, washed with ethanol (1 x 25ml) and
the solvent was removed under vacuum to give the title
compound (1.48g, 98%) as a white solid (*cis/trans ca 2:1*); mp
69-73°C; m/z (CI) 243 (M⁺).

15 6. [cis/trans-1-(tert-Butyloxycarbonylamino)cyclobutan-3-yl]acetaldehyde

To a cooled (-79°C) and stirred solution of the product
from the previous step (1.46g, 6.0mmol) in anhydrous toluene
20 (90ml) was added dropwise *via* cannula diisobutylaluminium
hydride (1M in toluene; 15ml) at such a rate as to maintain the
internal temperature below -78°C (ca 18 minutes). The resulting
mixture was stirred at -80°C for 1 hour before anhydrous
methanol (4.9ml) was added dropwise at such a rate as to
25 maintain the temperature below -78°C. Aqueous citric acid
(10%; 75ml) was added and the mixture was allowed to warm to
room temperature. Products were extracted with ethyl acetate (3
x 100ml), washed with brine (1 x 70ml), dried ($MgSO_4$) and
concentrated. Flash chromatography of the residue (silica gel,
30 hexane-ethyl acetate, 60:40) gave 1.22g (95%) of the title
aldehyde as a thick colourless oil which solidified on standing; δ
(250MHz, $CDCl_3$) 11.25 (1H, s, -CHO); m/z (CI) 212 (M⁺ -1).

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7. 3-[trans-1-(Dimethylamino)cyclobutan-3-yl]-5-[(1,2,4-triazol-1-yl)methyl]-1H-indole and 3-[cis-1-(Dimethylamino)cyclobutan-3-yl]-5-[(1,2,4-triazol-1-yl)methyl]-1H-indole.
Hydrogen oxalates.

5

To a solution of the aldehyde from the previous step (1.06g, 4.97mmol) in absolute ethanol (2.5ml) was added 4% aqueous sulfuric acid (5ml) followed by 1-(4-hydrazinophenyl) methyl-1,2,4-triazole dihydrochloride (1.3g, 4.97mmol). After being stirred for 1 minute, 4% aqueous sulfuric acid (40ml) was slowly added over 5 minutes and the reaction mixture was refluxed for 1 hour and 20 minutes. After being cooled to room temperature, methanol (100ml) was added and the mixture was basified with saturated aqueous potassium carbonate (20ml). The precipitated solids were filtered off, washed with methanol (2 x 30ml) and solvents were removed under vacuum. The remaining residue was triturated with hot ethanol (50ml) and the undissolved solid was removed by filtration and washed with ethanol (2 x 30ml). The resulting clear filtrate was concentrated under vacuum and the residue was purified by flash chromatography (silica gel, dichloromethane-methanol-ammonia, 85:15:1.5) to give 545mg (41%) of 3-(1-aminocyclobutan-3-yl)-5-[(1,2,4-triazol-1-yl)methyl]-1H-indole as a mixture of *cis* and *trans* isomers.

10

15
20
25
30

To a cooled (0°C) and stirred solution of *cis/trans*-3-(1-aminocyclobutan-3-yl)-5-[(1,2,4-triazol-1-yl)methyl]-1H-indole (270mg, 1.0mmol) in anhydrous methanol (20ml) were added sodium cyanoborohydride (127mg, 2.0mmol), glacial acetic acid (289µl, 5.0mmol) and a solution of formaldehyde (38% w/v aqueous solution; 200µl) in absolute methanol (3ml). The reaction mixture was then allowed to warm to room temperature and it was stirred for 1.5 hours before saturated aqueous potassium carbonate (10ml) was added and

- 66 -

the methanol was removed under vacuum. The aqueous residue was extracted with ethyl acetate (3 x 50ml) and the combined organic solutions were washed with brine (2 x 15ml), dried (Na_2SO_4) and concentrated. The remaining residue was purified by preparative
5 TLC (silica gel, dichloromethane-methanol-ammonia, 90:10:1) to give 102mg (34%) of 3-[*cis*-1-(dimethylamino)cyclobutan-3-yl]-5-[(1,2,4-triazol-1-yl)methyl]-1H-indole (less polar isomer) and 132mg (44%) of 3-[*trans*-1-(dimethylamino)cyclobutan-3-yl]-5-[(1,2,4-triazol-1-yl)methyl]-1H-indole (more polar isomer). The hydrogen oxalate salts
10 were prepared and showed:

Cis-ISOMER: mp 223-226°C (ethanol-methanol); δ (250MHz, D_2O) 8.54 (1H, s, Ar-H), 8.05 (1H, s, Ar-H), 7.63 (1H, br d, Ar-H), 7.50 (1H, d, $J = 8.4\text{Hz}$, Ar-H), 7.28 (1H, s, Ar-H), 7.20 (1H, dd, $J = 8.4$ and 1.8Hz , Ar-H), 5.50 (2H, s, Ar- CH_2), 3.82-3.68 (1H, m, -CH-), 3.54-3.36 (1H, m, -CH-), 2.96-2.80 (8H, m and s, - CH_2 - and -NMe₂), 2.36-2.20 (2H, m, - CH_2 -). (Found: C, 59.20; H, 6.37; N, 17.78. $\text{C}_{17}\text{H}_{21}\text{N}_5 \times 1.0 \text{C}_2\text{H}_2\text{O}_4$ requires: C, 59.21; H, 6.02; N, 18.17%).

20
Trans-ISOMER: mp 137-139°C (ethanol); δ (250MHz, D_2O) 8.54 (1H, s, Ar-H), 8.05 (1H, s, Ar-H), 7.54 (1H, br s, Ar-H), 7.51 (1H, d, $J = 8.5\text{Hz}$, Ar-H), 7.35 (1H, s, Ar-H), 7.22 (1H, dd, $J = 8.5$ and 1.8Hz , Ar-H), 5.49 (2H, s, Ar- CH_2 -), 3.94-3.66 (2H, m, -CH-), 2.84-2.66 (8H, s and m, -NMe₂ and - CH_2 -), 2.62-2.48 (2H, m, - CH_2 -); m/z (CI) 296 ($\text{M}^+ + 1$). (Found: C, 59.33; H, 6.28; N, 17.82. $\text{C}_{17}\text{H}_{21}\text{N}_5 \times 1.0 \text{C}_2\text{H}_2\text{O}_4$ requires: C, 59.21; H, 6.02; N, 18.17%).

30 An X-ray crystal structure was obtained for the *cis*-ISOMER hydrogen oxalate which confirmed the initial assignment based on nOe experiments carried out on the free bases.

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EXAMPLE 7

N-2-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]ethylazetidine.

Oxalate. 1.6 Hydrate

5

A mixture of Intermediate 1 (0.75g, 4.3mmol) and 4'-(1,2,4-triazol-4-yl)phenylhydrazine (0.75g, 4.3mmol), in 4% H₂SO₄ (50ml) was heated at reflux for 22h. The mixture was cooled to room temperature, basified with K₂CO₃ and extracted with EtOAc (3 x

10 100ml). The resultant crude product was chromatographed on silica gel eluting with CH₂Cl₂/MeOH/NH₃ (40:8:1) to give the title-product (0.12g). The oxalate hydrate salt was prepared; mp 218-220°C. (Found: C, 52.86; H, 5.63; N, 17.98. C₁₇H₁₅N₅.C₂H₂O₄ 1.6H₂O requires C, 52.87; H, 5.79; N, 18.13%). δ (360MHz, D₂O)

15 2.36-2.63 (2H, m, CH₂), 3.06 (2H, t, J=7.0Hz, CH₂), 3.52 (2H, t, J=7.0Hz, CH₂), 4.01-4.22 (4H, m, 2 of CH₂), 7.21 (1H, dd, J=2.0 and 8.6Hz, Ar-H), 7.39 (1H, s, Ar-H), 7.56 (1H, d, J=8.6Hz, Ar-H), 7.62 (1H, d, J=2.0Hz, Ar-H), 8.91 (2H, s, Ar-H).

20

EXAMPLE 8

N-2-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]ethylpyrrolidine.

Oxalate

25

INTERMEDIATE 8

4-(1-Pyrrolidinyl)butanal diethylacetal

A solution of 4-chlorobutanal diethylacetal (10g, 55.40mmol) in pyrrolidine (40ml) was heated at reflux for 16h. The solvent was removed under vacuum, 2N NaOH (50ml) added and the mixture extracted with CH₂Cl₂ (100ml). The extract was dried and evaporated and the residue distilled (74°C, 1mmHg) to give the

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title-product (8.8g, 74%). δ (250MHz, D₆-DMSO) 1.10 (6H, t, J=7.5Hz, 2 of CH₃), 1.34-1.70 (8H, m, 4 of CH₂), 2.28-2.40 (6H, m, 3 of CH₂), 3.26-3.60 (4H, m, 2 of CH₂O), 4.46 (1H, t, J=5.5Hz, CHO).

5 N-2-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]ethylpyrrolidine.

Oxalate

10 The title-compound was prepared from Intermediates 6 and 8 using the procedure described for Example 7. The oxalate salt was prepared; mp 244-245°C; (Found: C, 62.25; H, 6.06; N, 21.33. C₁₈H₁₉N₅. 0.5(C₂H₂O₄) 0.1H₂O requires C, 62.22; H, 6.20; N, 21.34%); δ (250MHz, D₂O) 1.78-1.86 (4H, m, 2 of CH₂), 2.86-3.08 (8H, m, 4 of CH₂), 7.32 (1H, dd, J=2.0 and 8.6Hz, Ar-H), 7.36 (1H, d, J=2.0Hz, Ar-H), 7.50 (1H, d, J=8.6Hz, Ar-H), 7.85 (1H, d, J=2.0Hz, Ar-H), 9.02 (2H, s, Ar-H), 11.18 (1H, s, indole NH).

EXAMPLE 9

Tablet Preparation

20 Tablets containing 1.0, 2.0, 25.0, 26.0, 50.0 and 100.0mg, respectively of the following compounds are prepared as illustrated below:

25 N-2-[5-(1,2,4-Triazol-1-ylmethyl)-1H-indol-3-yl]ethyl azetidine.
Hydrogen Oxalate.

N-2-[5-(1,2,4-Triazol-1-yl)-1H-indol-3-yl]ethylazetidine.

Bisoxalate

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N-Methyl-3-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]
methyldazetidine. 0.65 Oxalate

5 \pm)N-Methyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]
methylpyrrolidine. Hydrogen Oxalate. 0.2 Hydrate

(2R)N-Methyl-2-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]
methylpyrrolidine. 1.3 Benzoate. 0.9 Hydrate

10 3-[*trans*-1-(Dimethylamino)cyclobutan-3-yl]-5-[(1,2,4-triazol-
1-yl) methyl]-1H-indole and 3-[*cis*-1-(Dimethylamino)cyclobutan-
3-yl]-5-[(1,2,4-triazol-1-yl)methyl]-1H-indole. Hydrogen
Oxalates.

15 N-2-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]ethylazetidine. Oxalate.
1.6 Hydrate

N-2-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]ethylpyrrolidine. Oxalate
20

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TABLE FOR DOSES CONTAINING FROM
1.25MG OF THE ACTIVE COMPOUND

	Amount-mg			
5	Active Compound	1.0	2.0	25.0
	Microcrystalline cellulose	49.25	48.75	37.25
	Modified food corn starch	49.25	48.75	37.25
	Magnesium stearate	0.50	0.50	0.50

10 TABLE FOR DOSES CONTAINING FROM
26-100MG OF THE ACTIVE COMPOUND

15	Active Compound	26.0	50.0	100.0
	Microcrystalline cellulose	52.0	100.0	200.0
	Modified food corn starch	2.21	4.25	8.5
	Magnesium stearate	0.39	0.75	1.5

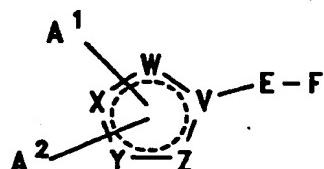
20 All of the active compound, cellulose, and a portion of the corn starch are mixed and granulated to 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active ingredient per tablet.

25

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CLAIMS:

- 5 1. A compound of formula I, or a salt or prodrug thereof:



(1)

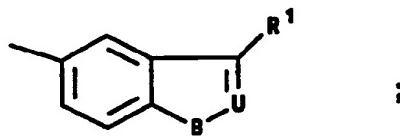
- 15 wherein the broken circle represents two non-adjacent double bonds in any position in the five-membered ring; two, three or four of V, W, X, Y and Z represent nitrogen and the remainder represent carbon provided that, when two of V, W, X, Y and Z represent nitrogen and the remainder represent carbon, then the 20 said nitrogen atoms are in non-adjacent positions within the five-membered ring;

25 A^1 represents hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, $-OR^X$, $-SR^X$, $-NR^XRY$, $-NR^XCORY$, $-NR^XCO_2RY$, $-NR^XSO_2RY$, or $-NR^ZCTNR^XRY$;

30 A^2 represents a non-bonded electron pair when four of V, W, X, Y and Z represent nitrogen and the other represents carbon; or, when two or three of V, W, X, Y and Z represent nitrogen and the remainder represent carbon, A^2 represents hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, $-OR^X$, $-SR^X$, $-NR^XRY$, $-NR^XCORY$, $-NR^XCO_2RY$, $-NR^XSO_2RY$, or $-NR^ZCTNR^XRY$;

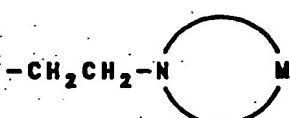
- 72 -

E represents a bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;
 F represents a group of formula

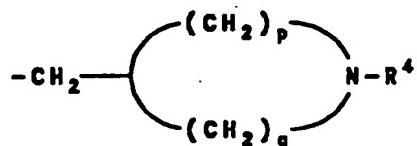


U represents nitrogen or C-R²;
 B represents oxygen, sulphur or N-R³;
 R¹ represents a group of formula (i), (ii) or

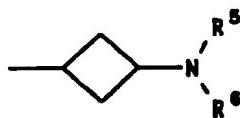
15 (iii):



(i)



(ii)



(iii)

in which

M represents the residue of an azetidine, pyrrolidine or piperidine ring;

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p is zero or 1 and q is an integer from 1 to 4,
provided that the sum of p+q is 2, 3 or 4;

R², R³, R⁴, R⁵ and R⁶ independently represent
hydrogen or C₁₋₆ alkyl;

5 R^X and R^Y independently represent hydrogen,
hydrocarbon or a heterocyclic group, or R^X and R^Y
together represent a C₂₋₆ alkylene group;

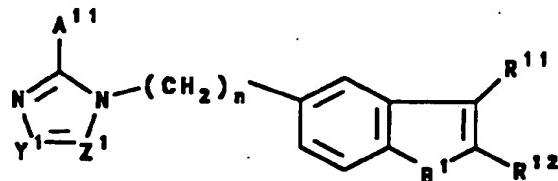
R^Z represents hydrogen, hydrocarbon or a
heterocyclic group;

10 T represents oxygen, sulphur or a group of
formula =N.G; and

G represents hydrocarbon, a heterocyclic group
or an electron-withdrawing group.

15 2. A compound of formula I as claimed in
claim 1, or a salt or prodrug thereof, wherein R¹
represents a group of formula (i) or (ii) as defined in
claim 1.

20 3. A compound as claimed in claim 1
represented by formula II, and salts and prodrugs
thereof:



(III)

wherein

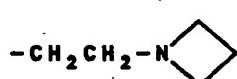
Y¹ represents nitrogen or A¹²-C;

Z¹ represents nitrogen or CH;

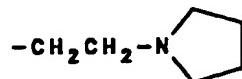
n is zero, 1, 2 or 3;

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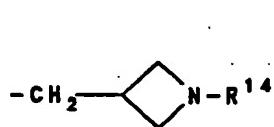
- B¹ represents oxygen, sulphur or N-R¹³;
A¹¹ and A¹² independently represent C₁₋₆ alkyl,
C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, aryl,
aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, heteroaryl,
5 heteroaryl(C₁₋₆)alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆
alkylamino or di(C₁₋₆)alkylamino, any of which groups may
be optionally substituted; or hydrogen, halogen, cyano,
trifluoromethyl or amino;
R¹¹ represents a group of formula (iv), (v),
10 (vi), (vii) or (viii):



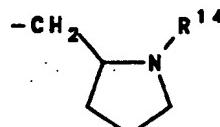
(iv)



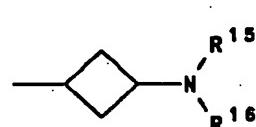
(v)



(vi)



(vii)



(viii)

- 25 and R¹², R¹³, R¹⁴, R¹⁵ and R¹⁶ independently
represent hydrogen or C₁₋₆ alkyl.

4. A compound as claimed in claim 3 wherein
A¹¹ and A¹² both represent hydrogen.

- 30 5. A compound as claimed in claim 3 or claim
4 wherein R¹² and R¹³ both represent hydrogen.

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6. A compound as claimed in any one of claims 3 to 5 wherein R¹⁴, R¹⁵ and R¹⁶ each represents methyl.

7. A compound as claimed in claim 1 selected
5 from:
N-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-
yl]ethylazetidine;
N-2-[5-(1,2,4-triazol-1-yl)-1H-indol-3-yl]ethylazetidine;
N-methyl-3-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-
10 yl]methylazetidine;
N-methyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-
yl]methylpyrrolidine;
(2R)-N-methyl-2-[5-(1,2,4-triazol-4-yl)-1H-indol-3-
yl]methylpyrrolidine;
15 3-[cis-1-(N,N-dimethylamino)cyclobutan-3-yl]-5-(1,2,4-
triazol-1-ylmethyl)-1H-indole;
3-[trans-1-(N,N-dimethylamino)cyclobutan-3-yl]-5-(1,2,4-
triazol-1-ylmethyl)-1H-indole;
N-2-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]ethylazetidine;
20 N-2-[5-(1,2,4-triazol-4-yl)-1H-indol-3-
yl]ethylpyrrolidine;
and salts and prodrugs thereof.

8. A pharmaceutical composition comprising a
25 compound of formula I as defined in claim 1 or a
pharmaceutically acceptable salt thereof or a prodrug
thereof in association with a pharmaceutically acceptable
carrier.

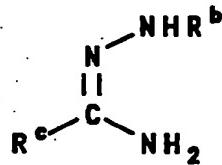
30 9. A compound of formula I as defined in
claim 1 or a pharmaceutically acceptable salt thereof or
a prodrug thereof for use in therapy.

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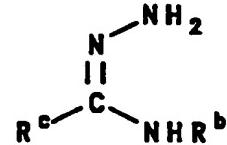
10. The use of a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof or a prodrug thereof for the manufacture of a medicament for the treatment and/or prevention of
 5 clinical conditions for which a selective agonist of 5-HT₁-like receptors is indicated.

10. A process for the preparation of a compound as claimed in any one of claims 1 to 7 which comprises:

15 (A) reacting a reactive derivative of a carboxylic acid of formula R^a-CO₂H with a compound either of formula III or of formula IV, or a salt thereof:



(III)

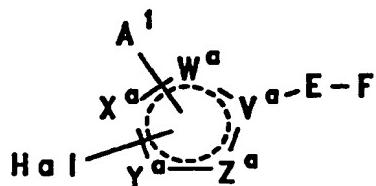


(IV)

25 wherein one of R^a, R^b and R^c is a group of formula A¹, another is a group of formula A², and the third is a group of formula -E-F, as defined in claim 1; or

(B) reacting a compound of formula XIV:

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(XIV)

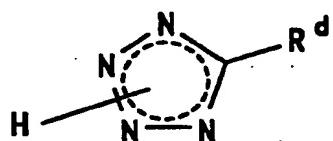
10 wherein A¹, E and F are as defined in claim 1, Hal represents halogen, and two of v^a, w^a, x^a, y^a and z^a, to one of which the group Hal is attached, represent carbon and the remainder represent nitrogen; with a reagent which provides an anion -A², where A² is as defined in
15 claim 1; or

(C) the cycloaddition of an alkyne of formula R^a-C≡C-R^b with an azide of formula R^c-N₃, where R^a, R^b and R^c are as defined above; or

20 (D) the cycloaddition of a nitrile of formula N≡C-R^d with an azide of formula R^e-N₃, where one of R^d and R^e represents a group of formula A¹ and the other is a group of formula -E-F, as defined in claim 1; or

25 (E) reacting a compound of formula R^e-L with a tetrazole derivative of formula XV:

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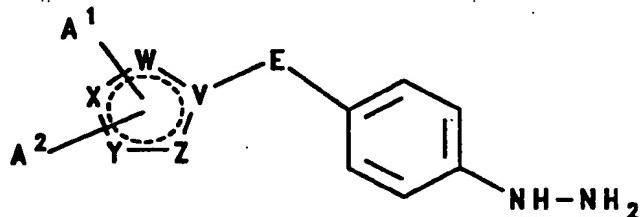
(XV)

wherein one of R^d and R^e represents a group of formula A¹
 10 and the other is a group of formula -E-F, as defined in
 claim 1, and L represents a suitable leaving group; in
 the presence of a base; or

(F) the cycloaddition of a nitrile of formula
 15 N=C-E-F, in which E and F are as defined in claim 1, with
 sodium azide, followed by acidification with a mineral
 acid; or

(G) reacting a compound of formula XVI:

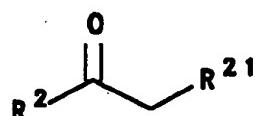
20



(XVI)

wherein V, W, X, Y, Z, A¹, A² and E are as defined in
 claim 1; with a compound of formula VII or a carbonyl-
 30 protected form thereof:

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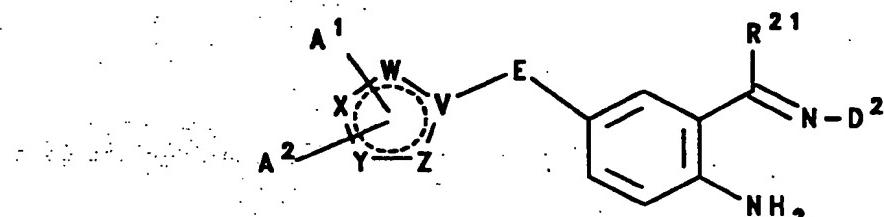
(VII)

wherein R^2 is as defined in claim 1 and R^{21} corresponds to the group R^1 as defined in claim 1 or represents a protected derivative thereof; followed by removal of any protecting groups present; and subsequently, where required, N-alkylation by standard methods to introduce the moieties R^3 and/or R^4 ; or

10

(H) cyclising a compound of formula XXV:

15



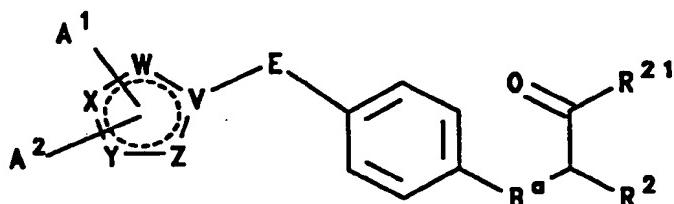
(XXV)

25 wherein V , W , X , Y , Z , A^1 , A^2 and E are as defined in claim 1, R^{21} is as defined above and D^2 represents a readily displaceable group; followed by removal of any protecting groups present; and subsequently, where required, N-alkylation by standard methods to introduce the moieties R^3 and/or R^4 ; or

30

(J) cyclising a compound of formula XXVIII:

- 80 -



(XXVIII)

wherein V, W, X, Y, Z, A¹, A², E and R² are as defined in
10 claim 1, R²¹ is as defined above, and B^a represents
oxygen or sulphur; followed by removal of any protecting
groups present; and subsequently, where required, N-
alkylation by standard methods to introduce the moiety
R⁴; and

15

(K) subsequently, where required, converting a
compound of formula I initially obtained into a further
compound of formula I by conventional methods.

20

12. A method for the treatment and/or
prevention of clinical conditions for which a selective
agonist of 5-HT₁-like receptors is indicated, which
method comprises administering to a patient in need of
such treatment an effective amount of a compound of
25 formula I as defined in claim 1, or a pharmaceutically
acceptable salt thereof or a prodrug thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 93/01495

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D403/14 C07D403/06 A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 313 397 (THE WELLCOME FOUNDATION LTD.) 26 April 1989 cited in the application see the whole document ----	1-12
Y	WO,A,91 18897 (THE WELLCOME FOUNDATION LTD.) 12 December 1991 cited in the application see the whole document ----	1-12
P,Y	EP,A,0 497 512 (MERCK SHARP & DOHME LTD.) 5 August 1992 cited in the application see the whole document -----	1-12

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

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- "O" document referring to an oral disclosure, use, exhibition or other means
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Date of the actual completion of the international search

3 November 1993

Date of mailing of the international search report

25. 11. 93

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patrimonium 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 93/01495

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		CN-A-	1064485	16-09-92
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